COUNTWAY LIBRARY
HC 3IIP 7

THE FRANCIS A. COUNTWAY LIBRARY OF MEDICINE
HARVARD MEDICAL LIBRARY-BOSTON MEDICAL LIBRARY

Digitized by the Internet Archive
in 2016

https://archive.org/details/westernjournalof1691cali

OFFICIAL JOURNAL OF

ARIZONA MEDICAL ASSOCIATION · CALIFORNIA MEDICAL ASSOCIATION · DENVER MEDICAL SOCIETY · IDAHO MEDICAL ASSOCIATION · NEVADA STATE MEDICAL ASSOCIATION · NEW MEXICO MEDICAL SOCIETY · UTAH MEDICAL ASSOCIATION · WASHINGTON STATE MEDICAL ASSOCIATION · WYOMING MEDICAL SOCIETY

DISPLAY SHELVES

The Western Journal of Medicine

VOLUME 169 • NUMBER 1 JULY 1998

ARTICLES

9 Prospective Evaluation of Risk Factors for Exercise-Induced Hypogonadism in Male Runners
S T SKARDA and M R BURGE

13 Association Between Facial Cutaneous Coccidioidomycosis and Meningitis
E L ARSURA, W B KILGORE, J W CALDWELL, J C FREEMAN, H E EINSTEIN, and R H JOHNSON

17 Invasive and Noninvasive Hemodynamic Monitoring of Patients with Cerebrovascular Accidents
G C VELMAHOS, C C J WO, D DEMETRIADES, M H BISHOP, and W C SHOEMAKER

CONFERENCES AND REVIEWS

23 Role of Clinicians in Cigarette Smoking Prevention
E J PÉREZ-STABLE and E FUENTES-AFFLICK

30 Excimer Laser Refractive Surgery
E E MANCHE, J D CARR, W W HAW, and P S HERSH

EPITOMES

39 Important Advances in Psychiatry

ALERTS, NOTICES, AND CASE REPORTS

46 Perils and Pitfalls in the Diagnosis of Cushing's Syndrome
K LOH, P A FITZGERALD, T R MILLER, and J B TYRRELL

COMMENTARY

51 In Search of the Fourth Maxim
J W GARDNER

53 Invisible Children
E O NIGHTINGALE and K HANNIBAL

Special Correspondence

FOLLOW UP LETTER

55 Response to the Commission on the Future of Medical Education from the University of California President R C Atkinson

LESSONS FROM THE PRACTICE

56 That Funny Feeling
W E BYRD

58 Focus on the Medical History
M V S ANDAVOLU

FRANCIS A. COUNTWAY LIBRARY OF MEDICINE BOSTON, MA
JUL 20 1998

OTHER FEATURES

1 Subscription Information
4 Continuing Medical Education Activities
60 Instructions for Authors
63 Classified Advertising

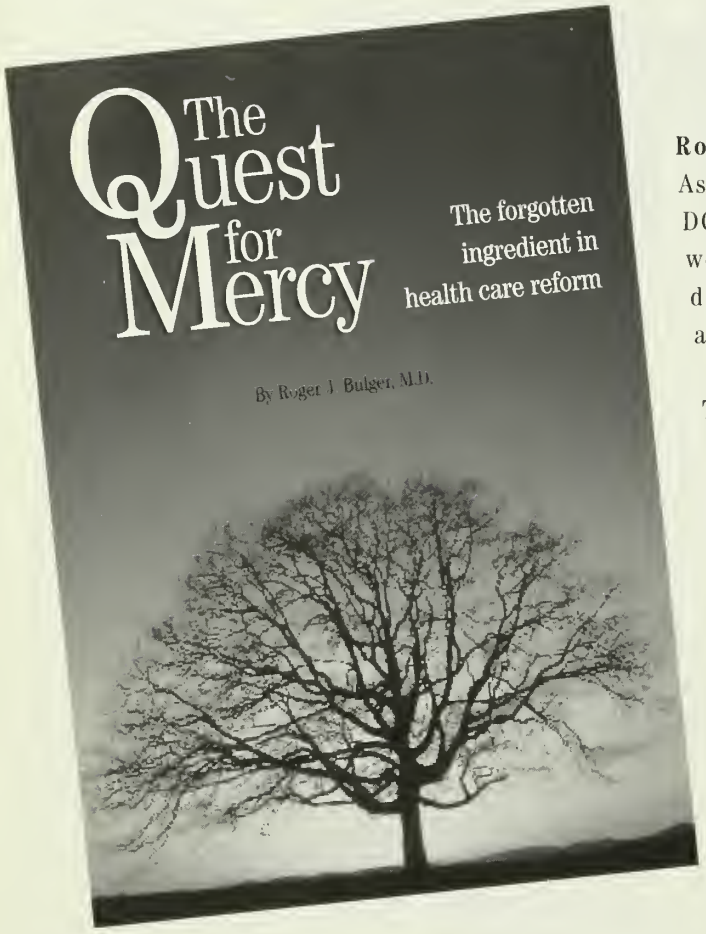
Detailed Table of Contents: 2, 3

Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Medical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology

The Quest for Mercy

The forgotten ingredient in health care reform

by Roger J. Bulger, MD, FACP



Roger J. Bulger, MD, FACP is President of the Association of Academic Health Centers in Washington, DC. He has published scores of papers and chapters, as well as three books on subjects ranging from infectious diseases to medical education, humanities, Hippocrates, and, of course, academic health centers.

The Quest for Mercy is aimed at physicians, including young physicians and medical students. The book addresses managed care and managed cost, sickness and healing, hope and despair, relationships, oaths, populations, prevention, and patients.

"This book will become a classic."

Linda Hawes Clever, MD
Editor, THE WESTERN JOURNAL OF MEDICINE

The Complete Manuscript As Published In
The Western Journal of Medicine

ORDER YOUR COPIES NOW!

Per Copy: $10.00*

*Note: USA/Canada postage and handling included, all other countries please add US $6.00 Air Printed Matter postage. Please add Virginia and local sales tax where applicable. Quantity discounts available; please call.

I would like to order_____copy(ies) of **The Quest For Mercy**.

Payment must accompany order. Total amount enclosed $_____

NAME _____

INSTITUTION _____

ADDRESS _____

CITY/STATE/ZIP _____

COUNTRY _____

❑ Check Enclosed $_____ *please charge my* ❑ VISA ❑ MASTERCARD
(*make payable to:* The Western Journal of Medicine)

Account #_____ Exp. date _____

Signature _____

MAIL TO: *The Western Journal of Medicine*, 1224 West Main Street, Suite 200, Charlottesville, Virginia 22903-2858
Phone: (804) 979-8034 • Fax: (804) 979-4025 • www.wjmed.com

CARDEN JENNINGS
PUBLISHING CO., LTD.

The Western Journal of Medicine®

SINCE 1902

CARDEN JENNINGS PUBLISHING COMPANY LTD

A PUBLICATION OF CARDEN JENNINGS PUBLISHING CO, LTD • 1224 WEST MAIN STREET, SUITE 200 • CHARLOTTESVILLE, VIRGINIA 22903-2858
TELEPHONE (804) 979-8034; FACSIMILE (804) 979-4025; E.MAIL wjm@cjp.com

LINDA HAWES CLEVER, MD, *Editor*
EDWARD D HARRIS JR, MD, *Associate Editor*
WILLIAM T CARDEN JR, *Publisher*

ALLISON SPEARMAN, *Managing Editor*
DAVID ERN, *Marketing Director*

SARAH BRUCE, *Senior Copy Editor*

editorial communications to DR CLEVER • business communications to MS SPEARMAN

Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Medical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

SPECIAL EDITORS

Special Editor for Arizona
Marshall B. Block, Phoenix, Ariz

Special Editor for Denver
David Shander, Denver, Colo

Special Editor for Idaho
E. R. W. Fox, Coeur d'Alene, Idaho

Special Editor for Nevada
Anton P. Sohn, Reno, Nev

Special Editor for New Mexico
I. Brian Taylor, Carlsbad, NM

Special Editor for Utah
C. Basil Williams, Salt Lake City, Utah

Special Editor for Washington
David Hopkins, Federal Way, Wash

Special Editor for Wyoming
Joseph P. Murphy, Casper, Wyo

ASSISTANT EDITORS

Clinical Investigation
H. Benfer Kaltreider

Health and Public Policy
Ralph Crawshaw

International Health
Anvar Velji

Lessons From the Practice
Stephen J. McPhee
Jonathan E. Rodnick

Medical Staff Conferences
Nathan M. Bass

Poetry
Margaret Kaufman

Primary Care Medicine
Stephen J. McPhee
Terrie Mendelson

Radiologic Cases
Jonathan M. Levy

JUL 20 1993

EDITORIAL BOARD

Editor Emeritus
Malcolm S. M. Watts, San Francisco, Calif

Anesthesiology
Carol Lake, Sacramento, Calif

Biostatistics and Epidemiology
Virginia L. Ernster, San Francisco, Calif

Cardiac and Thoracic Surgery
Norman E. Shumway, Stanford, Calif

Dermatology
Clifton R. White Jr, Portland, Ore

Emergency Medicine
William A. Boehm, Alamogordo, NM

General and Family Practice
Norman Kahn, Kansas City, Mo
Thomas E. Norris, Seattle, Wash
Joe Schoeber, Casper, Wyo

Internal Medicine
Albert Deisseroth, Houston, Texas
Alan Fogleman, Los Angelas, Calif
Patricia Gabow, Denver, Colo
John H. Holbrook, Salt Lake City, Utah
Philip Hopewell, San Francisco, Calif
Irwin J. Schatz, Honolulu, Hawaii
Walter E. Stamm, Seattle, Wash
Reginald Strickland, Albuquerque, NM
Stephen I. Wasserman, San Diego, Calif

Neurology
Robert Collins, Los Angeles, Calif
John Greenlee, Salt Lake City, Utah
Leslie Wiener, Los Angeles, Calif
Earl Zimmerman, Portland, Ore

Neurosurgery
George A. Ojemann, Seattle, Wash
Robert F. Spetzler, Phoenix, Ariz

Nuclear Medicine
Jerold M. Lowenstein, San Francisco, Calif

Obstetrics and Gynecology
Daniel Mishell Jr, Los Angeles, Calif

Occupational Medicine
Linda Rosenstock, Washington, DC

Ophthalmology
Sandy Feldman, La Jolla, Calif

Orthopedics
Thomas DeCoster, Albuquerque, NM

Pathology
Ronald Weinstein, Tuczon, Ariz

Pediatrics
Allen W. Mathies Jr, Pasadena, Calif
Diane Wara, San Francisco, Calif

Pharmacology
Rubin Bressler, Tucson, Ariz

Physical Medicine and Rehabilitation
Julie G. Madorsky, Pomona, Calif

Preventive Medicine and Public Health
Joseph L. Lyon, Salt Lake City, Utah

Psychiatry
J. Christian Gillin, San Diego, Calif
Lewis Judd, La Jolla, Calif

Radiology
Gary Glazer, Stanford, Calif
Michael L. Manco-Johnson, Denver, Colo
Albert A. Moss, Seattle, Wash

Surgery
Haile T. Debas, San Francisco, Calif
Alex G. Little, Las Vegas, Nev

Urology
Linda Shortliffe, Stanford, Calif

Senior Members at Large
Thomas Elmendorf, Davis, Calif
Edgar Waybum, San Francisco, Calif

ADVISORY BOARD, CLINICAL INVESTIGATION

Brian A. Cason, San Francisco, Calif
John Christenson, Salt Lake City, Utah
Kari Connolly, San Francisco, Calif
Bruce W. Goldberg, Portland, Ore
Philip Goodman, Reno, Nev
Roy Jones, Albuquerque, NM
Howard Lien, Tucson, Ariz
Barbara M. Lippe, Los Angeles, Calif
Michael W. McDermott, San Francisco, Calif
Jeanette Mladenovic, Denver, Colo
Kenneth M. Moser, San Diego, Calif
James C. Orcutt, Seattle, Wash
John Owings, Sacramento, Calif
Robert Robbins, Stanford, Calif
Henry Rosen, Seattle, Wash
Mary H. Samuels, Portland, Ore
George A. Sarosi, San Jose, Calif
Jeffrey Saver, Los Angeles, Calif
David Schriger, Los Angeles, Calif
Jack H. Simon, Denver, Colo
Peggy Sue Weintrub, San Francisco, Calif
Owen M. Wolkowitz, San Francisco, Calif

DISPLAY & CLASSIFIED ADVERTISING INFORMATION

CONTACT: MJ Mrvica Associates, Inc, 2 West Taunton Ave, Berlin, NJ 08009 • (609) 768-9360/FAX (609) 753-0064
Advertisements—The journal is published the second week of the month. Display advertising must be received no later than the first of the month preceding issue. Advertising rates will be sent on request. Acceptance of advertising is contingent upon approval by the Publisher.
The journal reserves the right to reject any advertisement.

SUBSCRIPTION INFORMATION

The subscription price per year is $65 in the United States and Canada (US funds); $80 in all other countries. Institutional rate $90. Single copies are $10. Special issues are $10. Address all subscription communications to:
THE WESTERN JOURNAL OF MEDICINE Circulation, 1224 W Main St, Suite 200, Charlottesville, VA 22903-2858 • Tel: (804) 979-8034

Allow six weeks for subscriptions to begin. Past issues must be bought individually. So long as reserve stocks are available, missing issue requests from subscribers are honored for up to six months after the issue date. Thereafter, the single copy rate of $10 is applicable for each issue available. Special issues are $10.

Change of Address—Requests for change of address should give both the old and new address. Allow six weeks for changeover.

SUBMITTING MANUSCRIPTS

Manuscripts for consideration should be sent to the managing editor, Allison Spearman, 1224 W Main St, Suite 200, Charlottesville, VA 22903-2858.

"Instructions for Authors"—A complete guide to manuscript submission and *WJM* style available from the publisher. Manuscripts may be prepared in accordance with the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals."

PUBLISHER

Copyright © 1998 by Carden Jennings Publishing Co, Ltd • Owned and Published by Carden Jennings Publishing Co, Ltd

All material subject to this copyright appearing in THE WESTERN JOURNAL OF MEDICINE may be photocopied for the noncommercial purpose of scientific or educational advancement. Volumes begin with January and July.

THE WESTERN JOURNAL OF MEDICINE (ISSN 0093-0415/USPS 084 480) is published monthly by Carden Jennings Publishing Co, Ltd, 1224 W Main St, Charlottesville, VA 22903-2858. Periodicals postage paid at Easton, Pennsylvania.

POSTMASTER: Send address changes to *The Western Journal of Medicine*, Circulation, 1224 W Main St, Suite 200, Charlottesville, VA 22903-2858.

The Western Journal of Medicine

VOLUME 169 • NUMBER 1 • JULY 1998

CONTENTS

ARTICLES

9 **Prospective Evaluation of Risk Factors for Exercise-Induced Hypogonadism in Male Runners**

SHAYNE T. SKARDA, MD, and MARK R. BURGE, MD

From the Division of Endocrinology and Metabolism, Department of Medicine, University of New Mexico School of Medicine, Albuquerque.

13 **Association Between Facial Cutaneous Coccidioidomycosis and Meningitis**

EDWARD L. ARSURA, MD; WILLIAM B. KILGORE; JOHN W. CALDWELL, PharmD; JAMES C. FREEMAN, MD; HANS E. EINSTEIN, MD; and ROYCE H. JOHNSON, MD

From the Veterans Affairs Medical Center, Salem, Virginia and the Department of Internal Medicine, Kern Medical Center, Bakersfield, California, an affiliate of the University of California–Los Angeles.

17 **Invasive and Noninvasive Hemodynamic Monitoring of Patients With Cerebrovascular Accidents**

GEORGE C. VELMAHOS, MD, PhD; CHARLES C.J. WO; DEMETRIOS DEMETRIADES, MD, PhD; MICHAEL H. BISHOP, DO; and WILLIAM C. SHOEMAKER, MD

From the Department of Emergency Medicine, King Drew Medical Center, and the Division of Trauma and Critical Care, Department of Surgery, University of Southern California Medical Center, Los Angeles.

CONFERENCES AND REVIEWS

23 **Role of Clinicians in Cigarette Smoking Prevention**

ELISEO J. PÉREZ-STABLE, MD, and ELENA FUENTES-AFFLICK, MD, MPH

From the Division of General Internal Medicine, Department of Medicine, the Departments of Pediatrics and of Epidemiology and Biostatistics, and the Medical Effectiveness Research Center for Diverse Populations, University of California San Francisco School of Medicine.

30 **Excimer Laser Refractive Surgery**

EDWARD E. MANCHE, MD; JONATHAN D. CARR, MD; WELDON W. HAW, MD; and PETER S. HERSH, MD

From the Departments of Ophthalmology, Stanford University School of Medicine, Stanford, California; Emory University School of Medicine, Atlanta, Georgia; and the University of Medicine and Dentistry of New Jersey–New Jersey Medical School, Newark, New Jersey.

EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

Psychiatry

Items of progress in psychiatry. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, as to both scientific fact and important clinical significance.

39 **Advances in Mood Stabilizing Medications**

BARTON J. BLINDER MD, PhD; SUVARNA BHAT, MD; and VISANT A. SANATHARA

40 **Traumatic Disorders—Contemporary Directions**

ANDREI NOVAC, MD

41 **When Chest Pain, Shortness of Breath, and Palpitations Are Not due to Cardiopulmonary Pathology**

IRWIN I. ROSENFELD, MD

42 **Treatment Update in Geriatric Psychiatry**

LON S. SCHNEIDER, MD

43 **The New Antipsychotic Compounds—Is a Clinical Choice Algorithm Possible?**
WILLIAM C. WIRSHING, MD

ALERTS, NOTICES, AND CASE REPORTS

46 **Perils and Pitfalls in the Diagnosis of Cushing's Syndrome**
KEH-CHUAN LOH, MRCP; PAUL A. FITZGERALD, MD; THEODORE R. MILLER, MD; and J. BLAKE TYRRELL, MD
From the Division of Endocrinology, Department of Medicine and Metabolic Research Unit, and the Department of Pathology, University of California San Francisco School of Medicine.

COMMENTARY

51 **In Search of the Fourth Maxim**
JOHN W. GARDNER
From the School of Education, Stanford University, Stanford, California.

53 **Invisible Children**
ELENA O. NIGHTINGALE, MD, PhD, and KARI HANNIBAL, MA
From the Institute of Medicine, National Research Council, Board on Children, Youth, and Families, Washington, DC, and The Albert Schweitzer Fellowship, Boston, Massachusetts.

CORRESPONDENCE

55 **Special Follow-Up Letter**
RICHARD C. ATKINSON
From the Office of the President, University of California, San Francisco, School of Medicine.

LESSONS FROM THE PRACTICE

56 **That Funny Feeling**
WILLIAM E. BYRD, MD
From Roanoke Valley Internal Medicine and Rheumatology, Roanoke Rapids, North Carolina.

58 **Focus on the Medical History**
MURTHY V.S. ANDAVOLU, MD
From the Department of Medical Oncology, Los Angeles County–University of Southern California Medical Center, Los Angeles, California

OTHER FEATURES

1 **Subscription Information**
4 **Continuing Medical Education Activities**
60 **Instructions for Authors**
63 **Classified Advertising**

★ Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

Continuing Medical Education

ARIZONA • CALIFORNIA, HAWAII, NEVADA • COLORADO • IDAHO • NEW MEXICO • UTAH • WASHINGTON • WYOMING

ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (520) 626-7832; (800) 328-5868.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Paulette Richardson, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-3387. For more information on accreditation or certification, please write to the above address.

ALLERGY/IMMUNOLOGY

August 6–9—**A Midsummer Night's Wheeze.** California Society of Allergy, Asthma, and Immunology at La Costa Resort and Spa, Carlsbad. Thurs.–Sun. 12 hrs. $145–$195. Contact: CSAAI (714) 828-8022.

CARDIOLOGY

August 13–15—**Critical Care Cardiology.** American College of Cardiology at Ritz-Carlton, San Francisco. Thurs.–Sat. 16.5 hrs. Contact: ACC, 9111 Old Georgetown Rd., Bethesda, MD 20814-1699, (800) 253-4636 ext. 695.

September 10–12—**Coronary Interventions 1998.** Scripps Clinic at Sheraton Grande Torrey Pines Hotel, La Jolla. Wed.–Sat. 28 hrs. Contact: Laurel Steigerwald, Scripps Clinic, Department of Academic Affairs, 403C, 10666 N. Torrey Pines Rd., La Jolla, CA 92037 (619) 554-8556.

September 14–18—**Cardiology Board Review.** UCSF at Cathedral Hill Hotel, San Francisco. $725. Contact: Postgraduate Programs, Box 0656, UCSF, San Francisco, CA 94143-0656.

October 8–10—**Cardiology Update 1998.** UCSF at Carmel Valley Ranch Resort, Carmel. Thurs.–Sat. 12 hrs. $485–$560. Contact: UCSF (415) 476-5208.

October 31—**Update in Electrocardiography and Arrythmias.** UCSF at Radisson Miyako Hotel, San Francisco. Sat. 7.5 hrs. $195. Contact: UCSF (415) 476-5208.

January 7-10, 1999—**NewEra Cardiac Care:Innovation and Technology.** Marriott's Mountain Shadows Resort, Scottsdale Arizona. Sponsored by the Cardiothoracic Research &Education Forum. Contact:Aligned Management Associates, Inc. P.O. Box 23220, San Diego CA 92193 (760) 751-8841. Fax (760) 751-8842. www.amainc.com

February 18-20, 1999—**19th Annual Pathophysiology & Techniques of Cardiopulmonary Bypass.** San Diego Marriott Hotel & Marina. Sponsored by the Cardiothoracic Research &Education Forum. Contact:Aligned Management Associates, Inc. P.O. Box 23220, San Diego CA 92193 (619) 541-1444 or fax (619-541-1447 www.amainc.com

EMERGENCY MEDICINE

August 9–12—**Essentials in Emergency Medicine and Urgent Care.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Sun.–Wed. Contact: CMEA P.O. Box 270469, San Diego, CA 92198-2469 or web: http://www.cmea.com.

August 17–18—**High Risk Emergency Medicine.** American College of Emergency Physicians at Marina Beach Marriott, Marina del Rey. Mon.–Tues. 15 hrs. $549. Contact: Center for Emergency Education, 5330 Primrose Dr., Ste. 250, Fair Oaks, CA 95628 (800) 651-CEME.

October 3-7—**National Conference on Wilderness and Travel Medicine.** AmericanCollege of Emergency Physicians at Pare Fifty Five Hotel, San Francisco, CA. 25 hrs. Credit. Contact: (888) 263-6338.

October 8–10—**17th Annual Advances in Pulmonary and Critical Care.** UCSF at Palace Hotel, San Francisco. Thurs.–Sat. 17 hrs. $495. Contact: UCSF (415) 476-5208.

October 19–20—**Trauma Uncensored: 1998.** UC Davis at Hyatt Regency, Sacramento. Mon.–Tue. Contact: (916) 734-5390.

October 19–23—**Emergency Medicine Symposium I.** UCSD at La Jolla Marriott, San Diego. Mon.–Fri. 32 hrs. $495. Contact: OCME (619) 534-3940.

October 26–30—**27th Annual Topics in Emergency Medicine.** UCSF at Radisson Miyako Hotel, San Francisco. Mon.–Fri. 32 hrs. $675. Contact: UCSF (415) 476-5208.

November 9–13—**Emergency Symposium III.** UCSD at La Jolla Marriott, San Diego. Mon.–Fri. 32 hrs. Contact: OCME (619) 534-3940.

December 14-18— **Emergency Symposium II.** UCSD at La Jolla Marriott, San Diego. Mon.–Fri. 32 hrs. Contact: OCME (619) 534-3940.

FAMILY PRACTICE/PRIMARY CARE

June 14–19—**21st Annual Fingers to the Toes Primary Care Orthopedics.** UC Davis at Stanford Sierra Camp, Fallen Leaf Lake. Sun.–Fri. 26 hrs. $495. Contact: UCD (916) 734-5490.

June 18–19—**Controversies in Women's Health. Topics in Primary Care.** UCLA at Sheraton Universal Hotel, Universal City. Thurs.–Fri. 11.5 hrs. $300. Contact: UCLA (310) 794-2620.

July 1–5—**The Orlando Primary Care Review Course.** Sponsored by Continuing Medical Education Associates. Buena Vista Palace, Orlando, FL. Wed.–Sun. 30 hrs. Credit: AMA, AOA, AAFP. $750. Contact: Victoria Gonzales, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

July 6–9—**Family Practice Board Review Course.** Fairmont Hotel, San Francisco. 25 hrs. $475 ($525 if postmarked after May 25). Contact: Program Coordinator, Dept. of Family and Community Medicine, UCSF School of Medicine, 500 Parnassus Ave., MU-3E, San Francisco 94143-0900. (415) 476-5250.

July 15–17—**17th Annual Conference on Child Abuse and Neglect.** UC Davis at Radisson Hotel, Sacramento. Wed.–Fri. $175. Contact: Office of CME UCD (916) 734-5390.

July 23–27—**Masters of Medicine.** Sponsored by Continuing Medical Education Associates. Marriott Marquis, New York, NY. Thurs.–Mon. 30 hrs. Credit: AMA, AOA, AAFP. $795. Contact: Victoria Gonzales, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

August 6–9—**Cardiology in Primary Care.** Sponsored by Continuing Medical Education Associates. Hotel del Coronado, San Diego, CA. Mon.–Thurs. 20 hrs. Credit: AMA, AOA, AAP, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

August 9–12—**Essentials in Emergency Medicine and Urgent Care.** Sponsored by Continuing Medical Education Associates. Hotel del Coronado, San Diego, CA. Thurs.–Sun. 20 hrs. Credit: AMA, AOA, AAFP. $575.

Contact: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

August 9–12—**Essentials in Emergency Medicine and Urgent Care.** Sponsored by Continuing Medical Education Associates. Hotel del Coronado, San Diego, CA. Thurs.–Sun. 20 hrs. Credit: AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

September 13-15—Health Care Leadership Institiute Physicans Leadership Program. Huntington Hotel, San Francisco, CA. Contact Laura Johnson-Morasch California Academy of Family Physicans (CAFP), 114 Sansome Street, Suite 1305, San Francisco, CA 94104-3824. (415) 394-9121 or fax (415 394-9119. email: HCL1@FamilyDocs.org

October 14–16—**13th Annual Primary Care Medicine: Principles and Practice.** UCSF at Cathedral Hill Hotel, San Francisco. Wed.–Fri. 20 hrs. $550. Contact: Postgraduate Programs, Box 0656, UCSF, San Francisco, CA 94143-0656. (415) 476-5208.

October 22–26—**Masters of Medicine.** Sponsored by Continuing Medical Education Associates. Marriott Marquis, New York, NY. Thurs.–Mon. 30 hrs. Credit: AMA, AOA, AAFP. $795. Contact: Victoria Gonzales, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

December 3-4—**Controversies in Women's Health.** UCSF at Cathedral Hill Hotel, San Francisco. Thurs.–Fri. 13 hrs. Credit. $370. Contact: UCSF (415)476-5208.

GERIATRICS

November 8–11—**Geriatrics Update 1998.** Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego, CA. Sun.–Wed. 20 hrs. Credit: AMA, AOA, AAFP. $525. Contact: Victoria Gonzales, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

IMMUNIZATION

INFECTIOUS DISEASE

November 5–8—**Advances in Infectious Disease.** Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego, CA. Thurs.–Sun. 20 hrs. Credit: AMA, AOA, AAFP. $525. Contact: Victoria Gonzales, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200; http://www.cmea.com

December 2–6—**Internal Medicine- 1998 Fall Program.** Sponsored by Continuing Medical Education Associates. Boca Raton Resort and Club, Boca Raton, FL. Wed.–Tues. 30 hrs. Credit: AMA, AOA, AAP, AAFP. $750. Contact: Victoria Gonzales, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

December 9—**AIDS-Associated Malignancies: Biology and Clinical Management.** UCSF at Palace Hotel, San Francisco. Wed. Credit 4.5 hours. $135. Contact: UCSF (415) 476-5208.

December 10-12—**Clinical Care of the AIDS Pateient**. UCSF at Palace Hotel, San Francisco. Thurs-Sat. Credit 24 hours. $455. Contact: UCSF (415) 476-5208.

INTERNAL MEDICINE

October 9–13—**Internal Medicine - 1998 Fall Program.** Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego, CA. Fri.–Tues. 30 hrs. Credit: AMA, AOA, AAP, AAFP. $750. Contact: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198-2469. (800) 993-2632 or (619) 674-5200. http//www.cmea.com.

KEY TO ABBREVIATIONS

DREW:	Charles R. Drew Postgraduate Medical School, Office of Continuing Medical Education, (213) 563-4800.
LLU:	Loma Linda University, Continuing Medical Education Programs, (909) 824-4963.
STAN:	Stanford University, Postgraduate Education. (415) 723-5594.
UCD:	University of California, Davis, Office of Continuing Medical Education, (916) 734-5390.
UCI:	University of California, Irvine, Memorial/UCI Center for Health Education, (714) 824-5926.
UCLA:	University of California, Los Angeles, Continuing Education in Medicine and Health Sciences, (310) 794-2620.
UCSD:	University of California, San Diego, Office of Continuing Medical Education, (619) 534-3940.
UCSF:	University of California, San Francisco, Extended Programs in Medical Education, (415) 476-4251.
USC:	University of Southern California, Postgraduate Division, (800) USC-1119.

MANAGED CARE

September 10–12—**Management of the Hospitalized Patient in the Managed Care Era.** UCSF at Palace Hotel, San Francisco. 20 hrs. $475. Contact: UCSF (415) 476-5208.

NEPHROLOGY

October 2–8—**13th Comprehensive Nephrology Review Course.** UCLA at Beverly Hilton Hotel, Beverly Hills. Fri-Thurs. 44.5 hrs. $800. Contact: UCLA (310) 794-2620.

NEUROLOGY

October 10—**Brain Attack'98** UCLA at Beverly Hilton Hotel, Beverly Hills,CA. Fee $85. Contact Sheryl Crowley, Office of Continuing Medical Education, UCLA School of Medicine. (310) 794-3324.

OB/GYN

October 23–27—**OB/GYN Review.** Red Lion Hotel, Glendale. $675. Sat.–Tues. 38 hrs. Contact: USC School of Medicine, Postgraduate Division, 1975 Zonal Ave., KAM 307, Los Angeles, CA 90033-1039; Phone (213) 342-2555 or (800) USC-1119; Fax (213) 342-2152 or (888) 665-8650; email usccme@hsc.usc.edu.

OCCUPATIONAL & ENVIRONMENTAL

August 6–7—**Occupational and Environmental Toxicology for the Health & Safety Professional.** University Health Services at Claremont Resort & Spa, Oakland. Thurs.–Fri. 12.5 hrs. $742-$950. Contact: Center for Occupational& Environmental Health, University of California, Berkeley, Richmond Field Station, 1301 S 46th St, Bldg 102, Richmond, CA 94804 (510) 231-5645.

August 6–7—**Synthesizing Office Workstation Ergonomics: Putting it all Together.** University Health Services at Claremont Resort & Spa, Oakland. Thurs.–Fri. 14 hrs. $742-$950. Contact: Center for Occupational& Environmental Health, University of California, Berkeley, Richmond Field Station, 1301 S 46th St, Bldg 102, Richmond, CA 94804 (510) 231-5645.

October 5–9—**Occupational and Environmental Medicine I.** UCSF at Radisson Miyako Hotel, San Francisco. Mon.–Fri. 40 hrs. $725. Contact: Postgraduate Programs, Box 0656, UCSF, San Francisco, CA 94143-0656. (415) 476-5208.

ONCOLOGY

September 11–12—**4th Annual Cancer Research Program.** UC Davis at Cancer Center Auditorium, Sacramento. Fri.–Sat. Contact: UCD (916) 734-5390.

September 24–26—**22nd Annual Physicians Cancer Symposium.** Scripps-Health at Sheraton San Diego Hotel & Marina. Thurs.–Sat. 16.5 hrs. $425–$450. Contact: Stevens Cancer Center, Scripps Memorial Hospital, 9888 Genesee Ave., La Jolla, CA 92037. Tuthanne Crawford (619) 626-6794.

PEDIATRICS

September 18–19—**California Society of Pediatric Cardiology.** UC Davis at Seascape Resort, Aptos. Fri.–Sat. Contact: UCD (916) 734-5390.

January29-31,1999—**37TH Clinical Conference Pediatric Anesthesiology.** Disneyland Hotel, 1150 W. Cerritos Avenue, Anaheim, CA 92802. Sponsored by The Pediatric Anesthesiology Foudation. $250-$295. Contact David J Steward, M.B., Program Director, Pediatric Anesthesiology Conference Box #3, Childrens Hospital Los Angeles, P.O. Box 54700, Los Angeles, CA 90054. (213) 669-2262 or fax (213) 660-8983.

RADIOLOGY

October 3–4—**Ultrasound Update: 1998.** UC Davis at Doubletree Hotel, Sacramento. Sat.–Sun. Contact: (916) 734-5390.

RHEUMATOLOGY

September 10–12—**Rheumatology Board Review.** UCSF at Radisson Miyako Hotel, San Francisco. Thurs.–Sat. 20 hrs. $225. Contact: UCSF (415) 476-5208.

SURGERY

September 11–12—**4th Annual Surgical Review Course.** UC Davis at Fairfield. Fri.–Sat. Contact: (916) 734-5390.

September 18—**4th Annual Surgical Review.** UC Davis at TAFT, Fairfield. Fri. Contact: (916) 734-7203.

GENERAL/MULTIDISCIPLINARY

September 3–6—**Growth Hormone Research Society.** UCSF at Marriott Hotel, San Francisco. Thurs.–Sun. Contact: (415) 476-5808.

October 26–28—**Telemedicine IV.** UC Davis at Hilton Hotel, Anaheim. Mon.–Wed. Contact: (916) 734-5390.

LOSS PREVENTION

July 22—**Preventing Medication-Related Malpractice Claims.** Medical Insurance Exchange of California. San Francisco Medical Society. 2 hrs. Free or $40 to non members. Contact: David Carp (800) 227-4527.

August 4—A **Quality Improvement Program to Protect Your Medical Practice.** Medical Insurance Exchange of California. at Newark-Fremont Hilton Hotel. Tues. 2 hrs. Free or $40 to non members. Contact: David Carp (800) 227-4527.

August 18—A **Quality Improvement Program to Protect Your Medical Practice.** Medical Insurance Exchange of California. at Embassy Suites Hotel Walnut Creek. Tues. 2 hrs. Free or $40 to non members. Contact: David Carp (800) 227-4527.

September 9—A **Quality Improvement Program to Protect Your Medical Practice.** Medical Insurance Exchange of California. at Corte Madera Best Western Hotel, Corte Madera. Wed. 2 hrs. Free or $40 to non members. Contact: David Carp (800) 227-4527.

October 13—**Preventing "Failure to Diagnose" Malpractice Claims.** Medical Insurance Exchange of California. at Doubletree Hotel, Redding. Tues. Free or $40 to non members. Contact: David Carp (800) 227-4527.

October 20—A **Quality Improvement Program to Protect Your Medical Practice.** Medical Insurance Exchange of California. at Holiday Inn Select, Fairfield. Tues 2 hrs. Free or $40 to non members. Contact: David Carp (800) 227-4527.

November 3—**Medical Records Documentation for Patient Safety and Physician Defensibility.** Medical Insurance Exchange of California. at Santa Fe Bar and Grill, Berkeley. Tues. Free or $40 to non members. Contact: David Carp (800) 227-4527.

November 10—**Preventing "Failure to Diagnose" Malpractice Claims.** Medical Insurance Exchange of California. at San Francisco Medical Society. Wed. Free or $40 to non members. Contact: David Carp (800) 227-4527.

November 11—**Medical Records Documentation for Patient Safety and Physician Defensibility.** Medical Insurance Exchange of California. at Embassy Suites Hotel, Walnut Creek. Wed. Free or $40 for non members. Contact: David Carp (800) 227-4527.

LEARNING SPANISH

July 31-August 3(Los Angeles); August 28-31(San Diego); September 18-21 (Los Angeles); October 2-5(San Diego); October 23-26(Los Angeles)—**Conversation in Spanish.** Maricopa Health System. 36 hrs. $695. Contact: Rios Associates (520) 881-3295; (619) 218-4875; Fax (520) 325-4258.

HOME STUDY/SELF ASSESSMENT

California Physicians' Legal Handbook Series. California Medical Association. Contact: CMA, PO Box 7690, San Francisco 94120-7690. (800) 882-1262.

Breast Cancer, Early Detection and Control. Texas Medical Association. **CD ROM**. $70. 2 hrs. Contact: Texas Medical Association, (800) 880-1300; http://www.texmed.org/health_science/hs_poep.html

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Second Wednesday of Each Month—**Cardiovascular Education Series.** St Anthony Hospital at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

February 4-6, 1999—**Neurology For The Non-Neurologist.** Hyatt Regency, Cancun Mexico. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

February 5-7, 1999—**Arrhythmias: Interptretation, Diagnosis & Management** MGM Grand, Las Vegas, NV Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

February 12-14, 1999—**Clinical Endocrinology For Primary Care Physicans.** Beaver Run Resort, Breckenridge, CO.Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

February 19-21, 1999—**Managing Respiratory Diseases.** Marriot's Casa Marina,Key West,FL. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

February 25-27, 1999—**Dermatology For The Non-Dermatologist.** Atlantis Paradise Resort, Bahamas. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

February 26-28, 1999—**Coronary Heart Disease Update.** Hilton Tapatio Cliffs, Scottsdale, AZ. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

March 12-14, 1999—**Dermatology For The Non-Dermatologist.**Riviera Hotel & Casino, Las Vegas, NV. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

March 25-27, 1999—**Neurology For The Non-Neurologist.** Grand Beach Resort, St. Thomas, USVI. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

March 25-27, 1999—**Clinical Endocrinology For Primary Care Physicans.** Marriott's Beach Resort, St. Grand Cayman. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

March 26-28, 1999—**Managing Respiratory Diseases.** Buena Vista Palace,Orlando,FL. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 8-10, 1999—**Coronary Heart Disease Update.** Hyatt Regency, Aruba Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 8-10, 1999—**Clinical Endocrinology For Primary Care Physicans.** The Westin Resort, St John, USVI. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303)

798-5731.

April 9-11, 1999—**Arrhythmias: Interptretation, Diagnosis &Management** Hilton Tapatio Cliffs, Scottsdale, AZ. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 9-11, 1999—**Neurology For The Non-Neurologist.** Marriott's Casa Marina, Key West, FL. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 23-25,1999—**Managing Respiratory Diseases.** Bally's, Las Vegas, NV. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 23-25,1999—**Dermatology For The Non-Dermatologist.** Parc Fifty-five, San Francisco, CA. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 30-May 2, 1999—**Dermatology For The Non-Dermatologist.** South Sea Plantation, Captiva Island, FL. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 30-May 2, **Clinical Endocrinology For Primary Care Physicans.** Hyatt Regency, New Orleans, LA. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

May 14-16, 1999—**Managing Respiratory Diseases.** Hilton Resort, Hilton Head, SC. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

May 14-16, 1999—**Neurology For The Non-Neurologist.** Bally's, Las Vegas, NV. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

IDAHO

The listing of continuing medical education programs in Idaho is compiled by the Ada County Medical Society. To list CME programs here, please send information at least two months in advance to: Ada County Medical Society, Inc. 305 W. Jefferson, PO Box 2668, Boise, Idaho 83701. (208) 336-2930.

Brochures, course information, and registration forms are available from the contact person or organization.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

July 30-August 2—**Imaging in Santa Fe.** La Fonda Hotel, Santa Fe, New Mexico. Credit 20 hrs. AMA. $695. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

August 3-6—**Point-Counterpoint: Breast Imaging in Transition.** Eldorado Hotel, Santa Fe, New Mexico. Credit Approx. 26 hrs.AMA. $650. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email; webmaster@ryalsmeet.com.

October 12-15—**Neuroradiology for the Practicing Radiologists--The Robert Jahnke Memorial Course.** Hotel Loretto, Santa Fe, New Mexico. Approx. 20 hrs.AMA. $695. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

Every First and Third Tuesday—**Building and Implementing Clinical Practice Guidelines at the Point of Care.** Contact: Thomas A. Naegele, DO, (505) 275-7267.

SATELLITE COURSES

Contact: Joe Treat or Jim Cato, Immunization Program, (505) 827-2366

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

July 11-18—**Update in Clinical Immunology, Microbiology, and Infectious Diseases.** Snow King Resort at Jackson Hole, Wyoming. 25 hrs Credit AMA. Contact: (801) 581-8664; fax (801) 581-3647; email Rosalie.Lammle@hsc.utah.edu.

July 12-18—**Summer Meeting on Neuroradiology and Musculoskeletal Imaging.** Bishops Lodge, Santa Fe, New Mexico. Credit 30 hours AMA. Contact: (801) 581-8664; fax (801) 581-3647; email: Rosalie.Lammle@hsc.edu.

August 19-21—**Clinical Computing for Integrated Health Care Networks.** Yarrow Hotel and Conference Center, Park City. Credit 21 hours AMA. Contact: (801) 581-8664; fax (801) 581-3647; email: Rosalie. Lammle@hsc.edu.

August 19-22—**Seminars in Clinical Computing: Update 1998.** Park City. 19 hrs. Credit: AMA, AAFP, nursing CEU. Contact: University of Utah Office of CME, 50 N. Medical Dr., Salt Lake City, UT 84132. (801) 581-8664; fax (801) 581-3647; email: Rosalie.Lammle@hsc.utah.edu.

September 11—**Ophthalmology--Clinical Faculty Day.** John Moran Eye Center, Salt Lake City. 7 hrs. Credit AMA. Contact: (801) 581-8664; fax (801) 581-3647; email: Rosalie.Lammle@ hsc.utah.edu.

September 17-20—**Innovative Techniques in Plastic Surgery.** Wort Hotel, Jackson, Wyoming. 16 hrs. Credit AMA. Contact: (801) 581-8664; fax (801) 581-3647; email: Rosalie.Lammle@hsc.utah.edu.

September 29-October 3—**International Workshop on Magnetic Resonance Angiography.** Prospector Square Hotel and Conference Center, Park City. Not designated Category 1. Contact: (801) 581-8664; fax (801) 581-3647; email: Rosalie.Lammle@hsc.utah.edu.

October 2-3—**Western Intermountain Neurological Organization.** University Park Hotel, Salt Lake City. 12 hrs. Credit AMA. Contact: (801) 581-8664; fax (801) 581-3647; email: Rosalie.Lammle@hsc.utah.edu.

October 9-11—**Intensive Interactive Head and Neck Imaging Course.** University Park Hotel, Salt Lake City. 23 hrs. Credit AMA PRA.October 6-8, Preconference mini-fellowship (limited to course attendees), University of Utah School of Medicine, Department of Radiology. Contact: (801) 581-8664; fax (801) 581-3647; email: Rosalie.Lammle@hsc.utah.edu.

MEDICAL GRAND ROUNDS

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics.** Contact: UUSM.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

July 10–12—**3rd Annual Laser and Facial Plastic Surgery Symposium With Live Surgery Observation.** Presented by Wayne F. Larrabee, Jr, MD. Swedish Medical Center, Glaser Auditorium, Seattle. 17 hrs. Contact: (206) 386-2755.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Ave, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 S Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 340-2058.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Ste 1100, Seattle, WA 98121. (206) 441-9762.

OTHER CME OPPORTUNITIES

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE. June 26–28, 1998—**Fortieth Annual Scientific Meeting of The American Association for the Study of Headache**. Sheraton Palace, San Francisco. Contact: (609) 845-1720.

AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE. November 6–8, 1998—**Scottsdale Headache Symposium**. Scottsdale at Marriott's Camelback Inn Resort & Spa. Contact: (609) 845-1720.

The Atopy Syndrome in the Third Millenium. October 2-3, 1998, Zurich, Switzerland, on the occasion of the 50th anniversary of the allergy unit at the Dept of Dermatology, University Hospital, Zurich, and in collaboration with the European Academy of Allergology and Clinical Immunology. Contact: Prof. Dr. B. Wüthrich, Zurich, 41-1-255-3079, fax 41-1-255-4431.

Breast Imaging Today and Tomorrow. November 2-5, 1998. The Ritz-Carlton Resort Hotel, Naples Florida. Credit 26 hrs. AMA. $650. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

Internal Derangements of Joints October 9-11, 1998. The Westin River North, Chicago, Illinois. Credit 19 hrs. AMA. $695. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

THE INTERNATIONAL SKELETAL SOCIETY.- September 9-12, 1998—**25th Annual Refresher Course: Diagnosis & Management of Musculoskeletal Disorders**. Jury's Hotel, Dublin, Ireland. Credit 25 hrs. AMA. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

Mt. Sanai 1998 Body Imaging Update. October 10-13, 1998. The Plaza Hotel, New York, NY. Credit 22.5 hrs. AMA. $695. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

Musculoskeletal MR. October 22-25, 1998. The Westin Resort Hotel, Hilton Head, South Carolina. Credit 18 hrs. AMA. $650. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

NOTICE

State Associations should send their CME listings for publication to:

Allison Spearman, Managing Editor
Western Journal of Medicine
1224 W Main St, Ste 200
Charlottesville, VA 22903-2858

(804) 979-8034 • Fax (804) 979-4025 • wjm@cjp.com

Articles

Prospective Evaluation of Risk Factors for Exercise-Induced Hypogonadism in Male Runners

SHAYNE T. SKARDA, MD *and* MARK R. BURGE, MD, *Albuquerque, New Mexico*

Exercise-induced hypogonadotropic hypogonadism is well recognized among female endurance athletes but is less commonly observed in male endurance athletes. We have reported a well-characterized case of severe acquired hypogonadotropic hypogonadism in a male distance runner with osteopenia, stress fracture, and sexual dysfunction. Using this case as an index, we hypothesized that the presence of 1 or more specific risk factors would prospectively identify male endurance athletes with exercise-induced hypogonadotropic hypogonadism. These include a history of stress fracture, sexual dysfunction, or the initiation of endurance exercise before age 18 years. We studied 28 male endurance runners younger than 50 years who ran more than 40 miles per week. Of these runners, 15 had 1 or more of the above risk factors (group 1), and the remaining 13 had none of the putative risk factors (group 2). A group of 10 sedentary control subjects was also studied (group 3). There was no difference between groups 1 and 2 in weekly training mileage. Group 1 was younger than group 2 (32±10 years versus 39±6 years, *P*<.05) and had a lower body mass index (22.4±1.9 kg per m^2 versus 23.9±2.2 kg per m^2, *P*<.05). By bioelectric impedance, preliminary data showed that group 1 had a reduced body fat content (group 1, 14.5%±2.8%; group 2, 16.9%±2.0%; and group 3, 17.5%±4.1%; *P*<.05). Fasting morning concentrations of free testosterone (group 1, 45.3 ± 26.4 pmol/l; group 2, 88.8 ± 24.3 pmol/l; and group 3, 69.1 ±21.5 pmol/l) and luteinizing hormone (group 1, 1.7±0.7 IU per liter; group 2, 2.0±1.1 IU per liter; and group 3, 1.9±0.6 IU per liter) did not differ among the groups (*P*>.05). One subject with primary hypogonadism was identified in group 1. The presence of the aforementioned risk factors does not predict the occurrence of exercise-induced hypogonadotropic hypogonadism among male endurance runners in this pilot study. A larger sample size or more discriminating risk factors (or both) may be necessary to identify this uncommon but potentially debilitating condition.

(Skarda ST, Burge MR. Prospective evaluation of risk factors for exercise-induced hypogonadism in male runners. West J Med 1998; 169:9–12)

Exercise-induced amenorrhea is a well-characterized clinical disorder among female athletes.[1,2] This condition is typified by acquired hypogonadotropic hypogonadism and has been associated with osteopenia and fractures.[1–5] Studies of sex hormone regulation in male athletes are less numerous, although evidence suggests that male endurance athletes have decreased levels of testosterone compared with sedentary controls.[6–11] Although clinically important hypogonadism has been reported rarely among male endurance athletes, most reported cases show normal or slightly decreased concentrations of serum luteinizing hormone (LH) in conjunction with low-normal concentrations of testosterone.[6,11,12] There have been few reports of clinically important hypogonadism in men due to exercise.[6,13–15] In addition, consideration must be given to the possibility of anabolic steroid abuse in all male athletes presenting with hypogonadotropic hypogonadism.[16]

Our group recently published a well-documented case of exercise-associated hypogonadotropic hypogonadism in a 29-year-old male marathon runner who presented with stress fractures of the hip and pelvis, severe osteopenia, and hypogonadotropic hypogonadism.[13] Treatment with clomiphene citrate returned sex hormone levels to the normal range, and the hypogonadal symptoms resolved. Using this observation as an index case for the current study, we hypothesized that exercise-induced hypogonadism in male endurance athletes

From the Division of Endocrinology and Metabolism, Department of Medicine, University of New Mexico School of Medicine, Albuquerque.

Reprint requests to Mark R. Burge, MD, Division of Endocrinology and Metabolism, Department of Medicine, University of New Mexico School of Medicine, Rm 5ACC, Albuquerque, NM 87131.

This research was supported in part by National Institutes of Health National Center for Research Resources grant No. 5M01-RR00997 from the University of New Mexico General Clinical Research Center.

ABBREVIATIONS USED IN TEXT

FT = free testosterone
LH = luteinizing hormone

may be identified by the presence of one or more specific risk factors. Specifically, we proposed that male runners with exercise-induced hypogonadism could be prospectively identified by the presence of the following characteristics seen in the index case:

- Intense exercise initiated before the attainment of sexual maturity,
- A history of stress fracture, and either or both
- Sexual dysfunction and
- Decreased libido.

Subjects and Methods

Subjects

Healthy male subjects were recruited by distributing a questionnaire at the 1995 Duke City Marathon, Albuquerque, New Mexico and to a local runners' club and through advertisements in the *University Daily Lobo*, the University of New Mexico, Albuquerque, campus newspaper. Inclusion criteria for runners stipulated that participants run at least 40 miles per week and be younger than 50 years. Of 85 questionnaires returned, 28 runners and 10 sedentary men met inclusion criteria and agreed to participate in the study. The study was approved by the University of New Mexico Human Research Review Committee, and informed consent was obtained from all study participants.

Questionnaire

Subjects completed a one-page questionnaire that quantitated the form, volume, and intensity of exercise. The presence or absence of the following "risk factors" was also ascertained: the initiation of endurance exercise before age 18 years (a surrogate for the attainment of sexual maturity); a previous history of stress fracture; and difficulty attaining erections, diminished sex drive since the initiation of exercise, or both. Fifteen runners in the study reported the presence of at least one of the putative risk factors and were included in group 1. Thirteen runners denied the presence of risk factors and were assigned to group 2. All study subjects denied past or present anabolic steroid abuse.

Ten sedentary control subjects were also studied. Sedentary levels of activity were determined on the basis of self-report using the Physical Activity Assessment Questionnaire.[17] Subjects with activity ratings of B or C (encompassing no regular physical activity or recreational physical activity only) were designated to be sedentary, and these subjects made up group 3.

Study Protocol

All participants reported to the University of New Mexico General Clinical Research Center in the morning following an overnight fast and abstinence from exercise for at least 24 hours for the determination of serum levels of LH, free testosterone (FT), and body composition.

Hormone Analysis

Luteinizing hormone levels were determined using the Coat-A-Count immunoradiometric assay kit (Diagnostic Products Corp, Los Angeles, California), which has a reference range of 1.4 to 11.1 IU per liter, an intra-assay coefficient of variation of 1.6%, and an interassay coefficient of variation of 7.1%. The sensitivity of the LH assay was approximately 0.15 IU per liter. Free testosterone levels were measured using the Coat-A-Count radioimmunoassay kit (Diagnostic Products Corp), which has a reference range of 62.5 pmol/l to 142.3pmol/l, an intra-assay coefficient of variation of 4.3%, an interassay coefficient of variation of 5.5%, and a sensitivity of 0.45 pmol/l.

Body Composition Analysis

Height and weight of subjects were obtained on the day a blood specimen was drawn. Body composition was determined with bioelectric impedance analysis (RJL Systems, Clinton Township, Michigan).[18]

Sample Size

An estimate of the power necessary to demonstrate a difference between groups 1 and 2 in the prevalence of exercise-induced hypogonadism was obtained using the equation for computing sample sizes for comparing two proportions.[19] Assuming a prevalence of exercise-induced hypogonadism of 30% in group 1 and 2% in group 2, 13 subjects were required in each group to demonstrate a significant difference between the groups with a 90% power and an α of .05.

Statistical Analysis

The two-tailed unpaired Student's *t* test was used to compare continuous variables, such as hormone concentrations. Proportional data, such as the presence or absence of hypogonadotropic hypogonadism, were compared using Fisher's exact test. Data are reported as the mean ± standard deviation, and figures depict the mean ± standard error.

Results

Subject Characteristics

Demographic and physical characteristics of the study subjects are summarized in Table 1. The subjects in group 1 were younger than those in group 2 and had a reduced body mass index compared with those in group 2. In addition, subjects in group 1 had a lower body fat content than those in groups 2 and 3.

Hormone Concentrations

One subject in group 1 exhibited sex hormone concentrations consistent with primary gonadal failure (LH,

TABLE 1.—*Demographic and Baseline Characteristics of Study Participants**

Participants	Age, yr	Weekly Mileage	Body Mass Index, kg/m²	Body Fat, %
Group 1 (n=14)	32 ± 10†	66.9 ± 29.5	22.4 ± 1.9†	14.4 ± 3.1†‡
Group 2 (n=13)	39 ± 6	52.7 ± 21.7	23.9 ± 2.2	16.8 ± 2.0
Group 3 (n=10)	39 ± 10	NA	23.2 ± 4.8	17.5 ± 4.1

NA = not available

*Data are reported as the mean ± standard deviation.
†P<.05 versus group 2.
‡P<.05 versus group 3.

15.9 IU per liter; and FT, 62.1 pmol/l [17.9 pg per ml]) and was excluded from analysis. As shown in Figure 1-A, LH values did not differ significantly among groups 1, 2, and 3. Similarly, there was no statistically significant difference in FT concentrations among the three groups (Figure 1-B).

To further assess the utility of our selected risk factors for predicting hypogonadotropic hypogonadism, we analyzed sex hormone concentrations of the affected runners (group 1) according to the risk factors they possessed: sexual dysfunction only, pubertal initiation of endurance exercise only, or having more than one risk factor. As shown in Figure 2-A and -B, there were no statistically significant differences in LH and FT concentrations among these three risk factor categories.

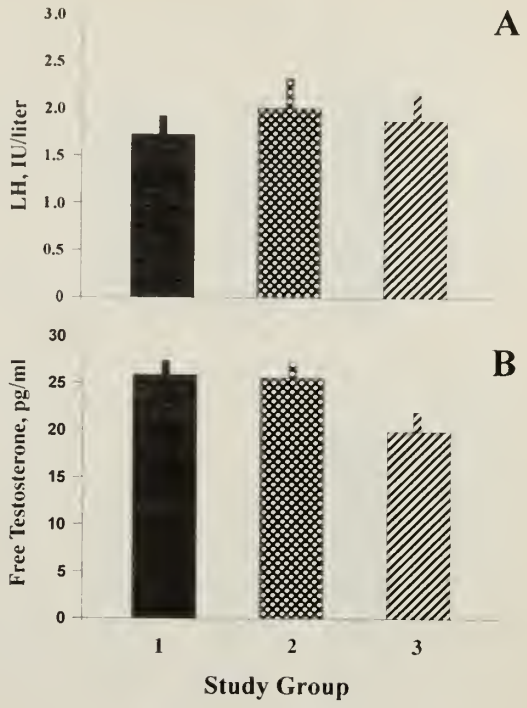


Figure 1.—Serum luteinizing hormone (LH) (A) and free testosterone (FT) (B) concentrations are shown for male endurance athletes with (group 1: LH, 2.8±4.0 IU/liter, and FT, 26.2±7.7 pg/ml) and without (group 2: LH, 2.0±1.1 IU/liter, and FT, 25.6±7.0 pg/ml) prospectively identified risk factors for exercise-induced hypogonadotropic hypogonadism, as well as sedentary control subjects (group 3: LH, 1.9±0.6 IU/liter, and FT, 19.9±16.2 pg/ml).

Discussion

It has been established that athletic amenorrhea is attributable to hypothalamic-pituitary dysfunction.[1,3,4,20] Given the central cause of this disorder, it is rational to expect that a similar disorder occurs in overzealous male athletes. The clinical manifestation of exercise-induced hypogonadism, however, is more readily apparent in women because of the intricate hormonal milieu necessary for normal cyclic menstruation. Men, on the other hand, may tolerate minor disturbances in sex hormone regulation without clinically apparent effects. Accordingly, numerous studies demonstrate that endurance exercise causes slight reductions in testosterone concentrations in men, but reports of clinically important hypogonadism attributable to exercise are uncommon.[6–10,21] Given, however, that this disorder may be associated with sexual dysfunction,[14,16,21] semen abnormalities,[6,8,14] muscle injury,[14] or osteopenia[16,22,23] (or any combination of all of these), identifying and preventing debilitating exercise-induced hypogonadism is desirable. Moreover, the prospective identification of a cohort of affected male athletes would allow the performance of controlled studies to clarify the natural history of the condition and to evaluate possible treatment options. Because exercise-induced hypogonadotropic hypogonadism appears to be rare in men, it is impractical to screen all male endurance athletes for this condition. Therefore, investigative attempts to identify sensitive indicators of the disease are appropriate.

Previous studies of sex hormone regulation in male athletes have not attempted to identify specific patient attributes that might predict the presence of acquired hypogonadotropic hypogonadism. This study evaluated the utility of specific, prospectively determined risk factors in identifying a subset of male endurance athletes who may be at high risk for the development of exercise-induced hypogonadism. No difference in sex hormone concentrations was observed among runners possessing at least one of the proposed risk factors and those who denied having them. This may reflect that the presence of risk factors alone is insufficient to identify cases of hypogonadotropic hypogonadism or that our assumptions of disease prevalence are incorrect, and a larger study population is necessary to demonstrate a difference.

A limitation of this study is the single-point measurement of hormone levels. Other studies have detected abnormal LH pulse frequency and amplitude in both men and women with normal mean LH, FT, and estradiol levels.[20,24] In addition, our exclusion of the person with evidence of primary gonadal failure by an elevated LH level may be inappropriate. Although exercise-

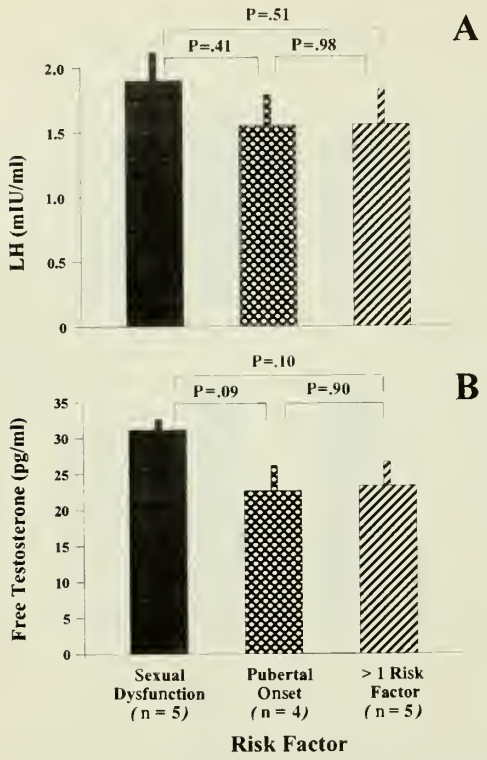


Figure 2.—Serum luteinizing hormone (LH) (A) and free testosterone (FT) (B) concentrations are shown according to risk factor among male endurance athletes having ≥1 putative risk factors for exercise-induced hypogonadotropic hypogonadism (group 1). The shaded bars denote sexual dysfunction (LH, 1.9±0.7 IU/liter, and FT, 31.1±2.6 pg/ml), the cross-hatched bars denote the start of endurance exercise before age 18 years (LH, 1.8±0.2 IU/liter, and FT, 25.7±9.0 pg/ml), and striped bars denote the presence of >1 risk factor, as described in the text (LH, 1.6±0.9 IU/liter, and FT, 23.3±8.4 pg/ml).

induced hypogonadotropic hypogonadism appears to be a centrally mediated condition, there are rare reports of elevated LH levels associated with decreased testosterone levels in male athletes.[24,25] The mechanism of this occurrence remains unclear, however.

The differences in LH and FT levels in the affected group of runners reporting only sexual dysfunction compared with other risk factors approach statistical significance (Figure 2). This implies that sexual dysfunction may be a less sensitive predictor of low testosterone levels in male runners than the other risk factors. That a true difference was not shown may represent a type II error that could possibly be remedied with a larger sample size.

Further study of the pathogenesis and prevalence of exercise-induced hypogonadotropic hypogonadism among male endurance athletes is clearly required. Research designed to sensitively identify affected athletes is a logical approach that may eventually advance our understanding of the condition. Considerations for future study design include a larger study population, an increased training mileage requirement, and the possible exclusion of sexual dysfunction alone as a risk factor. Finally, the utility of semen quality should be investigated as an additional factor for the possible identification of men debilitated by endurance exercise.

REFERENCES

1. Keizer H, Rogol A. Physical exercise and menstrual cycle alterations: what are the mechanisms? Sports Med 1990; 10:218–235

2. Yen S. Female hypogonadotropic hypogonadism. Endocrinol Metab Clin North Am 1993; 22:29–58

3. Fisher E, Nelson M, Frontera W, Turksoy R, Evans W. Bone mineral content and levels of gonadotropins and estrogens in amenorrheic running women. J Clin Endocrinol Metab 1986; 62:1232–1236

4. Baker E, Mathur R, Kirk R, Williamson H. Female runners and secondary amenorrhea: correlation with age, parity, mileage, and plasma hormonal and sex-hormone-binding globulin concentrations. Fertil Steril 1981; 36:183–187

5. Lindberg J, Fears W, Hunt M, Powell M, Boll D, Wade C. Exercise-induced amenorrhea and bone mineral density. Ann Intern Med 1984; 101:647–648

6. Ayers JW, Komesu Y, Romani T, Ansbacher R. Anthropomorphic, hormonal, and psychologic correlates of semen quality in endurance-trained male athletes. Fertil Steril 1985; 43:917–921

7. Wheeler G, Wall S, Belcastro A, Cumming D. Reduced serum testosterone and prolactin levels in male distance runners. JAMA 1984; 252:514–516

8. Arce JC, De Souza MJ, Pescatello LS, Luciano AA. Subclinical alterations in hormone and semen profile in athletes. Fertil Steril 1993; 59:398–404

9. Wheeler G, Singh M, Pierce D, Epling W, Cumming D. Endurance training decreases serum testosterone levels in men without change in luteinizing hormone pulsatile release. J Clin Endocrinol Metab 1991; 72:422–425

10. Smith R, Rutherford O. Spine and total body bone mineral density and serum testosterone in male athletes. Eur J Appl Physiol 1993; 67:330–334

11. Duclos M, Corcuff J, Rashedi M, Fougere V, Manier G. Does functional alteration of the gonadotropic axis occur in endurance trained athletes during and after exercise? Eur J Appl Physiol 1996; 73:427–433

12. Cumming D, Wheeler G, McColl E. The effects of exercise on reproductive function in men. Sports Med 1989; 7:1–17

13. Burge MR, Lanzi RA, Skarda ST, Eaton RP. Idiopathic hypogonadotropic hypogonadism in a male runner is reversed by clomiphene citrate. Fertil Steril 1997; 67:783–785

14. Naessens G, DeSlypere J, Dijs H, Driessens M. Hypogonadism as a cause of recurrent muscle injury in a high level soccer player. Int J Sports Med 1995; 16:413–417

15. Strauss R, Lanese R, Malarkey W. Decreased testosterone and libido with severe weight loss. Phys Sports Med 1993; 21:64–71

16. Bickelman C, Ferries L, Eaton RP. Impotence related to anabolic steroid use in a body builder—Response to clomiphene citrate. West J Med 1995; 162:158–160

17. Blair SN. Measurement of physical activity. In: Brownell KD, Fairburn CG, eds. Eating Disorders and obesity: a comprehensive handbook. New York (NY): Guilford Press; 1995:111–116

18. Lukaski HC, Bolonchuk WW, Hall CB, Siders WA. Validation of tetrapolar bioelectrical impedance method to assess human body composition. J Appl Physiol 1986; 60:1327–1332

19. Dawson-Saunders B, Trapp R. Basic and clinical biostatistics. 1st ed. Norwalk (Conn): Appleton & Lange; 1990

20. MacConnie SE, Barkan A, Lampman RM, Schork MA, Beitins IZ. Decreased hypothalamic gonadotropin-releasing hormone secretion in male marathon runners. N Engl J Med 1986; 315:411–417

21. Celani M, Grandi M. The pituitary-testicular axis in nonprofessional soccer players. Exp Clin Endocrinol 1989; 94:244–252

22. Griffith R, Dressendorfer R, Fullbright C, Wade C. Testicular function during exhaustive endurance training. Physician Sports Med 1990; 18:54–64

23. Bilanin J, Blanchard M, Russek-Cohen E. Lower vertebral bone density in male long distance runners. Sci Sports Exerc 1989; 21:66–70

24. Veldhuis JD, Evans WS, Demers LM, Thorner MO, Wakat D, Rogol AD. Altered neuroendocrine regulation of gonadotropin secretion in women distance runners. J Clin Endocrinol Metab 1985; 61:557–563

25. Hackney A, Sinning W, Bruot B. Reproductive hormonal profiles of endurance-trained and untrained males. Med Sci Sports Exerc 1988; 20:60–65

Articles

Association Between Facial Cutaneous Coccidioidomycosis and Meningitis

EDWARD L. ARSURA, MD, *Salem, Virginia*; WILLIAM B. KILGORE; JOHN W. CALDWELL, PharmD; JAMES C. FREEMAN, MD; HANS E. EINSTEIN, MD; *and* ROYCE H. JOHNSON, MD, *Bakersfield, California*

The skin is frequently a site of extrapulmonary dissemination in patients with coccidioidomycosis. Clinical experience in an endemic area suggests an association between facial cutaneous coccidioidomycosis and meningitis. Awareness of this association is important because coccidioidal meningitis is the most ominous site of spread in coccidioidomycosis. In this study, we assess whether cutaneous dissemination involving the face is associated with meningitis to a greater degree than that limited to the body. We retrospectively reviewed the medical records of 201 patients from 1987 to 1996 with disseminated coccidioidomycosis and found 30 patients with cutaneous involvement. Their mean age was 29.5±11.6 years; 20 patients were male; 14 were African American, 12 were Hispanic, 3 were white, and 1 was Asian. Nineteen patients had facial involvement, and 11 had isolated body involvement. Meningitis developed in 11 patients, 10 with facial involvement and 1 with only body involvement. Patients with facial lesions were more likely to have meningitis (odds ratio, 11.1; 95% confidence interval, 1.1 to 529, *P*=.023). The identification of a subgroup of patients at significant risk of developing meningitis may allow earlier detection and perhaps improved management of patients with meningeal disease.

(Arsura EL, Kilgore WB, Caldwell JW, Freeman JC, Einstein HE, Johnson RH. Association between facial cutaneous coccidioidomycosis and meningitis. West J Med 1998; 169:13–16)

Symptomatic infection with the pathogenic fungus *Coccidioides immitis* may present with a variety of clinical syndromes, but it usually manifests with self-limiting pulmonary symptoms.[1–6] Extrapulmonary dissemination occurs in about 5% of symptomatic cases,[7–9] leading to substantial morbidity and mortality.[1] The skin is a frequent site of extrapulmonary spread[6,10] and provides identifiable evidence of dissemination. The development of coccidioidal meningitis is an ominous event,[11,12] being fatal within two years if untreated.[3,13,14] In the medical literature, an association between cutaneous coccidioidal dissemination and coccidioidal meningitis has not been described. Our experience with coccidioidomycosis in the southern San Joaquin Valley of California has suggested an association between coccidioidal skin lesions, specifically facial lesions, and meningitis.

Before the 1991 to 1993 coccidioidomycosis epidemic in the Central Valley of California, the few patients with skin involvement made a study of this group difficult. During the epidemic, a growing number of patients with skin lesions allowed an analysis of the association between facial lesions and meningitis. In this study, we assess the frequency of meningitis in patients with facial skin lesions and compare these patients to those with body-only lesions. The identification of patients at a substantial risk of developing meningitis may allow early the detection and treatment of meningeal disease.

Patients and Methods

We did a retrospective medical record review of all patients (N = 201) in whom disseminated coccidioidomycosis developed from 1987 to 1996. Patients were observed at Kern Medical Center (n=184), Bakersfield, California, a 270-bed public hospital in the southern San Joaquin Valley, or in the practice of an infectious diseases specialist, RHJ, (n = 17). Of the 30 patients included in the study, 29 originated from Kern Medical Center. The study was approved by the Kern Medical Center Institutional Review Board.

The diagnosis of coccidioidomycosis was made if patients had a compatible symptomatic illness accompanied by positive results on a serologic test. The serologic

From the Department of Internal Medicine, Kern Medical Center, Bakersfield, California, an affiliate of the University of California Los Angeles. Dr Arsura is now with the Veterans Affairs Medical Center, Salem, Virginia.

Reprint requests to Edward L. Arsura, MD, Veterans Affairs Medical Center, 1970 Roanoke Blvd, Salem, VA 24153.

TABLE 1.—*Demographics and Complement Fixation (CF) Titers of Patients With Cutaneous Coccidioidomycosis*

Variable	Group		
	Overall	Facial Involvement	Body Involvement
Number of patients	30	19	11
Sex			
Male	20	13	7
Female	10	6	4
Mean (±SD) age, yr	29.5 (±11.6)	30.4 (±12.4)	28.0 (±10.5)
Race			
African American	14	9	5
Asian American	1	—	1
White	3	1	2
Hispanic	12	9	3
Modal CF titer*	1:256	1:256	1:256

*Titers ranged from 1:2 to 1:512 for all groups.

test was performed by the Kern County Public Health Laboratory and was considered positive by the presence of any immunoglobulin M antibody, as detected by immunodiffusion assay or the presence of a complement fixation titer of 1:4 or greater. Coccidioidal meningitis was diagnosed by a characteristic clinical course, the identification of lymphocytic pleocytosis, and a positive complement fixation titer in the cerebrospinal fluid.

Skin involvement was defined as cutaneous coccidioidal infection demonstrated by culture or the presence of endosporulating spherules in pathologic specimens. *C immitis* was identified on specimens stained with Gomori's methenamine-silver stain of at least one lesion in all patients. None of the patients' skin lesions were solely immunologic manifestations of coccidioidomycosis (erythema nodosum or erythema multiforme).

Patients were categorized according to the location of their lesions: One group had facial involvement (only or with concomitant body involvement), and the second had only body involvement. Facial involvement was defined as any lesion on or above the mandible and body involvement as any lesion below the mandible. Lesions were described as plaques, nodules, ulcers, pustules, or verrucous eruptions. Patient demographics were described.

The association between meningitis and the location of cutaneous lesions was estimated with the odds ratio (calculated with the statistical software program Epi Info, Version 5 [Centers for Disease Control and Prevention, Atlanta, Georgia]), using the exact method for determining the confidence interval. The *P* associated with Fisher's exact test is given.

Results

Of the 201 patients with disseminated coccidioidomycosis who we observed, 30 (15%) were identified with coccidioidal skin involvement. Nineteen patients (63%) had facial involvement, and 11 (37%) had involvement of the body alone. Of the patients with facial involvement, 5 (26%) had facial involvement in isolation and 14 (74%) had concomitant body involvement. Patient characteristics are given in Table 1.

Meningitis developed in 11 (37%) of the patients with skin involvement (Table 2). Meningitis developed in 10 patients (53%) with facial involvement and 1 patient (9%) with body involvement (odds ratio, 11.1; 95% confidence interval, 1.1 to 529; P=.023). Of the patients with facial involvement and meningitis, 3 had facial involvement only, and 7 had face and body involvement.

Clinical Features

Seventeen patients presented with pulmonary symptoms, and skin lesions developed a mean (±standard deviation) of 2.8 (±2.9) months later. Eight patients presented with concurrent clinical symptoms and skin lesions. Five patients had no pulmonary symptoms or had uncertain histories. Of the 11 patients in whom meningitis developed, 6 had skin lesions before having meningitis (5 for 1 to 4 months, and 1 for 2 years); 3 had pulmonary disease for two to five months before meningitis developed; 1 had pulmonary disease for a month before skin lesions, and meningitis developed five months later; and in 1 patient, skin lesions developed two months after the patient had meningitis. Five patients had skin lesions develop during their pregnancy. Serologic tests were negative for the human immunodeficiency virus in the 23 patients in whom they were performed.

Chest radiographic findings were abnormal in 23 cases. A diffuse pulmonary process was the most common finding (11 patients [37%]), followed by hilar adenopathy (5 patients [17%]), lobar infiltrate (3 patients [10%]), pleural effusion (3 patients), and cavities (1 patient [3%]). Ten patients had bone involvement, and seven of these also had facial lesions. Two patients had evidence of joint disease, and two had prominent lymph node involvement. Four patients with meningitis had dissemination to additional sites.

Patients were observed for a mean of 40.4 (±26.1) months. The first patient included was first seen in 1987, and 20 were diagnosed during the epidemic (1991 to 1993). Nineteen patients are still being observed. Three patients died; all had facial involvement, and two had meningitis. Four patients had no further follow-up after symptoms resolved after a mean of 25.8 (±5.9) months. Three patients were unavailable for follow-up, and one was transferred to a different physician

Treatment

Of the 19 patients without meningitis, 12 received amphotericin B with fluconazole maintenance therapy. Four patients received fluconazole alone. Treatment of the 11 patients with meningitis included the administration of intravenous amphotericin B in 10 patients (6 also received amphotericin B intrathecally), and 1 patient was treated with fluconazole. As maintenance therapy, three patients with meningitis received amphotericin B

TABLE 2.—*Demographics and Clinical Features of Patients With Meningitis*

Patient	*Lesion Location**	*Sex*	*Race*	*Age, yr†*	*CF titer*	*CSF titer*
1	Body	Female	Hispanic	17	1:256	1:1
2	Face and body	Female	Hispanic	24	1:128	1:64
3	Face and body	Female	African American	48	1:256	1:64
4	Face and body	Female	Hispanic	24	1:64	1:8
5	Face and body	Female	Hispanic	32	1:256	1:16
6	Face	Female	African American	20	1:8	1:16
7	Face	Male	African American	32	1:32	1:256
8	Face	Male	Hispanic	28	1:64	1:512
9	Face and body	Male	White	19	1:256	1:256
10	Face and body	Male	Hispanic	28	1:512	1:512
11	Face and body	Male	Hispanic	23	1:32	1:1

CF = complement fixation, CSF = cerebrospinal fluid

*Patients with lesions on their faces were 11.1 times more likely to have meningitis (95% confidence interval, 1.1 to 529, P=.023).
†Mean±standard deviation, 26.8 ± 8.6 years.

intrathecally, five received amphotericin B and fluconazole, and three received fluconazole alone.

Discussion

The epidemic of 1991 to 1993 highlighted *C immitis* as an extremely important pathogen.[6,15–18] Increased travel through endemic areas has caused cases of coccidioidomycosis to appear throughout the United States.[2,4,19] Increased morbidity and mortality are associated with more severe forms of pulmonary disease and with dissemination, particularly to the meninges.[11,12]

Our study allows clinicians to identify a subgroup of patients who may be at substantial risk of meningeal spread and is the largest study of patients with the cutaneous dissemination of coccidioidomycosis.

Patients with cutaneous dissemination represented 15% of the 201 patients with disseminated coccidioidomycosis observed during this time. Of our patients with skin involvement, meningitis developed in 11 (37%), which is similar to the traditional rate of 33% to 50% cited in the literature for any form of disseminated coccidioidomycosis.[10–12] Meningitis is not more or less likely to develop in patients with skin lesions compared to patients with other forms of dissemination. Patients with facial lesions were about 11 times more likely to have meningitis than patients with only body involvement. Of the patients with facial involvement, 10 (53%) had meningitis. Of the patients with only body involvement, meningitis developed in 1 (9%).

The reason for the association between facial cutaneous dissemination and meningitis is unclear. Perhaps patients with facial involvement have a higher concentration of organisms in a distribution that predisposes them to the development of meningeal involvement. *C immitis* reaches extrapulmonary locations such as the skin through hematogenous spread,[2,6] and drainage of these lesions into venous structures that articulate with the meninges is possible.

Some anomalies were noted in our study, including the overrepresentation of Hispanics with meningitis. Of the 12 Hispanics, 9 had facial lesions, and meningitis developed in 7 of them. In contrast, of the 14 African Americans, 9 had facial lesions, but meningitis developed in only 3. This may be an artifact of the patient base of Kern Medical Center or of the referral pattern. Meningitis developed in more women than men in our study, which differs from the male predominance noted in other coccidioidal meningitis studies.[11,12] The reason for this is unknown, but it may be attributed to our study that specifically examined patients with skin involvement. Of the patients examined, 5 (17%) had skin lesions during pregnancy.

With knowledge of this association, it becomes important to educate clinicians in the identification of skin lesions associated with coccidioidomycosis. Coccidioidal skin lesions do not have great specificity, and lesions such as papules and pustules are seen in many other skin conditions. Five of our patients had papular lesions or pustular lesions that could easily be overlooked, especially outside endemic areas.

Determining the clinical importance of facial skin lesions in a patient with coccidioidomycosis requires further study. Perhaps a patient with facial lesions should be treated proactively with a drug that crosses the blood-brain barrier and for a longer time than a person who has dissemination not involving such a high-risk area. Many factors such as age, sex, ethnicity, skin test reactivity, serologic test result, and response to therapy are important in deciding which therapeutic agent to give or the duration of treatment. As with any patient with disseminated disease, but more important in patients with facial skin involvement, a lumbar puncture is a mandatory part of the evaluation and can be helpful to a clinician in guiding therapy. A lumbar puncture may also be useful before the discontinuation of therapy.

Although this study is subject to the limitations of retrospective studies, it has clinical validity, and it is the

largest study of patients with cutaneous dissemination of coccidioidomycosis.

REFERENCES

1. Smith CE, Beard RR, Whiting EG, Rosenberger HG. Varieties of coccidioidal infection in relation to the epidemiology and control of the disease. Am J Public Health 1946; 36:1394–1402

2. Ample NM, Wieden MA, Galgiani JN. Coccidioidomycosis: clinical update. Rev Infect Dis 1989; 11:897–911

3. Drutz DJ, Catanzaro A. Coccidioidomycosis: part II. Am Rev Respir Dis 1978; 117:727–771

4. Stevens DA. Coccidioidomycosis. N Engl J Med 1995; 332:1077–1082

5. Quimby SR, Connolly SM, Winkelman RK, Smilack JD. Clinicopathologic spectrum of specific cutaneous lesions of disseminated coccidioidomycosis. J Am Acad Dermatol 1992; 26:79–85

6. Galgiani JN. Coccidioidomycosis. West J Med 1993; 159:153–171

7. Pappagianis D. Epidemiology of coccidioidomycosis. Curr Top Med Mycol 1988; 2:199–238

8. Pappagianis D, Einstein H. Tempest from Tehachapi takes toll or coccidioides conveyed aloft and afar. West J Med 1978; 129:527–530

9. Johnson RH, Caldwell JW, Welch G, Einstein HE. The great coccidioidomycosis epidemic: clinical features. In: Einstein HE, Catanzaro A, eds. Coccidioidomycosis—Proceedings of the 5th International Conference, August 24-27, 1994, Stanford University, Stanford, California. Washington (DC): National Foundation for Infectious Diseases; 1996:77–87

10. Knoper SR, Galgiani JN. Coccidioidomycosis. Infect Dis Clin North Am 1988; 2:861–875

11. Bouza E, Dreyer JS, Hewitt WL, Meyer RD. Coccidioidal meningitis: an analysis of thirty-one cases and review of the literature. Medicine (Baltimore) 1981; 60:139–172

12. Johnson RH, Brown JF Jr, Holeman CW, Helvie SJ, Einstein HE. Coccidioidal meningitis: a 25-year experience with 194 patients. In: Einstein HE, Catanzaro A, eds. Coccidioidomycosis—Proceedings of the 4th International Conference on Coccidioidomycosis, March 14-17, 1984, San Diego, California. Washington (DC): National Foundation for Infectious Diseases; 1985:411–421

13. Buss WC, Gibson TE, Gifford MA. Coccidioidomycosis of the ninges. Calif Med 1950; 72:167–169

14. Vincent T, Galgiani JN, Huppert M, Salkin D. The natural history of coccidioidal meningitis: VA–Armed Forces Cooperative Studies, 1955-1958. Clin Infect Dis 1993; 16:247–254

15. Einstein HE, Johnson RH. Coccidioidomycosis: new aspects of epidemiology and therapy. Clin Infect Dis 1993; 16:349–356

16. Update: Coccidioidomycosis–California, 1991-1993. MMWR Morb Mortal Wkly Rep 1994; 43:421–423

17. Olson PE, Bone WD, LaBarre RC, Martin CR, Utz GC, Miller LK, et al. Coccidioidomycosis in California: regional outbreak, global diagnostic challenge. Milit Med 1995; 6:304–308

18. Pappagianis D. Marked increase in cases of coccidioidomycosis in California: 1991, 1992, and 1993. Clin Infect Dis 1994; 19:S14–S18

19. Hobbs ER. Coccidioidomycosis. Dermatol Clin 1989; 7:227–239

Invasive and Noninvasive Hemodynamic Monitoring of Patients With Cerebrovascular Accidents

GEORGE C. VELMAHOS, MD, PhD; CHARLES C. J. WO; DEMETRIOS DEMETRIADES, MD, PhD; MICHAEL H. BISHOP, DO; *and* WILLIAM C. SHOEMAKER, MD, *Los Angeles, California*

Seventeen patients with hemodynamic instability from acute cerebrovascular accidents were evaluated shortly after arrival at the emergency department of a university-run county hospital with both invasive Swan-Ganz pulmonary artery catheter placement and a new, noninvasive, thoracic electrical bioimpedance device. Values were recorded and temporal patterns of survivors and nonsurvivors were described. Cardiac indices obtained simultaneously by the 2 techniques were compared. Of the 17 patients, 11 (65%) died. Survivors had higher values than nonsurvivors for mean arterial pressure, cardiac index, and oxygen saturation, delivery, and consumption at comparable times. Cardiac index values, as measured by invasive and noninvasive methods, were correlated. We concluded that hemodynamic monitoring in an acute care setting may recognize temporal circulatory patterns associated with outcome. Noninvasive electrical bioimpedance technology offers a new method for early hemodynamic evaluation. Further research in this area is warranted.

(Velmahos GC, Wo CCJ, Demetriades D, Bishop MH, Shoemaker WC. Invasive and noninvasive hemodynamic monitoring of patients with cerebrovascular accidents. West J Med 1998; 169:17–22)

Hemodynamics after stroke usually are initially evaluated by noting the blood pressure, skin color, pulse rate, temperature, respiratory rate, and mental status. Subsequent circulatory monitoring is often limited to blood pressure and heart rate recording, plus occasional arterial blood gas measurements and determinations of hematocrits and urinary output rates.

The temporal progression of the clinical status of central nervous system disorders is routinely assessed by evaluating neurologic signs and symptoms and by radiography, computed tomography, and magnetic resonance imaging. Progression of an anatomic lesion of the brain should be evaluated separately from the associated circulatory deficiencies, however, because low-flow shock and increased intracerebral pressure may limit cerebral blood flow, oxygenation, and metabolism. Except in extreme conditions, the blood pressure and the heart rate are not well correlated with blood flow in acute clinical situations[1]; the routine criteria for the early recognition of shock are subjective and imprecisely reflect underlying physiologic problems.[2]

The measurement of hemodynamic variables by invasive pulmonary artery balloon-tipped thermodilution (Swan-Ganz) catheters has been the criterion standard for evaluating circulatory function in critically ill patients. Although this technology is expensive, time-consuming, and personnel-intensive, it provides maximal hemodynamic monitoring that can be used at the bedsides of comatose patients in an emergency department (ED) shortly after admission. Substantial cost, complication rates, and logistic problems, however, prevent its being routinely used in the acute care setting.

Cardiac output monitoring by an electrical bioimpedance technique is emerging as a new method of monitoring hemodynamics that can be used anywhere in a hospital.[3] Its ease of application, combined with continuous on-line displays of data, may greatly affect hemodynamic monitoring. Handelsman extensively reviewed the noninvasive electrical bioimpedance methods for measuring cardiac output and concluded that they relate changes in thoracic electrical conductivity to changes in aortic blood volume and blood flow,[4] but their application to specific disease categories has not been confirmed. Recently, a new thoracic electrical bioimpedance device was described by Wang and colleagues at Drexel University, Philadelphia, Pennsylvania, and

From the Department of Emergency Medicine, King-Drew Medical Center (Mr Wo and Drs Bishop and Shoemaker), and the Division of Trauma and Critical Care, Department of Surgery, Los Angeles County-University of Southern California (LAC-USC) Medical Center (Drs Velmahos, Demetriades, and Shoemaker and Mr Wo), Los Angeles.

The authors have no commercial, proprietary, or financial interest in the product or company described in this article. Renaissance Technologies kindly loaned the machine to the authors for use during this study.

Reprint requests to George C. Velmahos, MD, PhD, Div of Trauma and Critical Care, Dept of Surgery, Los Angeles County–USC Medical Center, 1200 N State St, Rm 9900, Los Angeles, CA 90033 (e-mail: velmahos@hsc.usc.edu).

ABBREVIATIONS USED IN TEXT

CI = cardiac index
ECG = electrocardiographic
ED = emergency department
$PtcO_2$ = partial pressure of transcutaneous oxygen
SaO_2 = oxygen saturation, arterial
VO_2 = oxygen consumption

commercially developed by Renaissance Technologies (Newtown, Pennsylvania).[5,6] The new system included technology from the defense industries, state-of-the-art hardware that provides more stable signals, and redesigned software that improves data analysis, processing, and management.[7]

In the present study, we evaluated the accuracy and reliability of this new technology compared with the standard thermodilution method for measuring cardiac output in critically ill stroke patients shortly after admission to an ED. We also evaluated the feasibility of multiple noninvasive monitoring systems to assess the three components of circulation: cardiac function, pulmonary function, and tissue perfusion.

Patients and Methods

Patients

We studied a consecutive series of 17 patients with hemodynamic instability from acute cerebrovascular accidents using invasive and noninvasive physiologic monitoring systems shortly after the patients were admitted to the ED. There were 13 men and 4 women; 6 patients survived. The patients' mean (±SD) age was 61.5 + 18.5 years. All patients had coma with evidence of acute circulatory failure or shock. The final diagnosis in all patients was acute thrombotic cerebrovascular accident. The study was approved by the hospital Institutional Review Board. Informed consent was obtained for all invasive monitoring by pulmonary artery catheter.

Invasive Hemodynamic and Oxygen Transport Measurements

Hemodynamic monitoring was performed using a radial artery catheter and a percutaneously placed 7F flow-directed pulmonary artery catheter. All measurements were made during relatively stable periods when a patient did not exhibit anxiety, restlessness, or agitation. Cardiac output and cardiac index were calculated by the thermodilution technique (cardiac output computer, Model 9520A, Baxter Edwards Laboratories, Santa Ana, California). Three to five measurements were taken and the results averaged. Intravascular pressures were calibrated against a mercury sphygmomanometer and were measured using the midthoracic level as the zero reference point. The pressure values at the end of more than three expirations were averaged. At the time of cardiac output determination, arterial and mixed venous blood specimens were obtained anaerobically in heparinized syringes, stored in iced water, and promptly analyzed for PO_2, PCO_2, and pH and arterial (SaO_2) and mixed venous oxygen saturation values. Arterial and mixed venous oxygen contents were calculated from the saturation and hemoglobin values, with corrections made for dissolved oxygen in the plasma. Cardiac index (CI), oxygen delivery, oxygen consumption (VO_2), and other derived variables were calculated by standard formulas. Each complete data set was taken within a two-minute period and keyed to the time of cardiac output measurement. All flow variables and flow-derived variables were indexed to body surface area.

Thoracic Electrical Bioimpedance Measurement of Cardiac Index

We used a prototype model of a new thoracic electrical bioimpedance device developed for clinical use from earlier research.[5–7] An array of 11 noninvasive, disposable, prewired hydrogen electrodes, designed to reduce electrical polarization time, were positioned on the skin: two injecting electrodes were placed on the side of the neck at the junction with the shoulders, and two other injecting electrodes were placed at the lateral aspect of the lower thorax at the level of the xiphisternal junction. Four sensing electrodes were placed 5 cm inside the area defined by the injecting electrodes. Three electrocardiographic (ECG) leads were placed across the precordium and left shoulder.

A 100-kHz, 4-mA alternating current was propagated through a patient's thorax by the paired outer electrodes, and the voltage was sensed by the paired inner electrodes to record the ECG, the baseline impedance (Z_0), the impedance waveform for each heartbeat (dZ), and the first derivative of the impedance waveform (dZ/dt). The filters for signal processing used an all-integer-coefficient filtering technology that allows fast signal processing using less computational power. The digital signal-processing technique uses time-frequency distribution (a modified Wigner distribution) with a high signal-to-noise ratio.[5] The digital signal processing identifies and measures the following events on the impedance tracing: the beginning of systole, the opening of the aortic valve, the maximum ventricular contraction (dZ/dt_{max}), closing of the aortic valve, and mitral valve opening. The ECG signal is also evaluated by a state-of-the-art digital signal-processing technique for detecting the standard R-R spikes and Q, S and T waves, which then are used to reconstruct the QRST signal. The maximum value of the dZ/dt signal during the cardiac cycle, dZ/dt_{max} was calculated and displayed. A touch-screen interface displayed the real-time waveforms and calculated values; stroke volume, heart rate, cardiac output, and cardiac index were routinely calculated and displayed.[3–8]

Pulse Oximetry

A standard pulse oximeter was attached to the left forefinger, and after a short warm-up period, values were recorded at frequent intervals. At appropriate times dur-

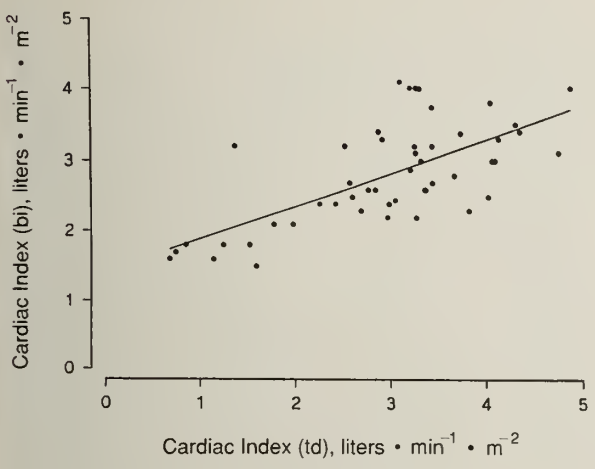


Figure 1.—Cardiac index values of bioimpedance (bi) are plotted against their simultaneously measured thermodilution (td) values.

ing the observation period, an arterial blood gas measurement was taken to compare the standard SaO_2 values with those obtained by pulse oximetry.

Transcutaneous Oxygen Tension

After calibration, a transcutaneous oxygen tension ($PtcO_2$) sensor, heated to 44°C to overcome local vasoconstriction, was placed on the left or right shoulder anteriorly. This sensor uses the same Clark polarographic electrode as is used in the standard blood-gas analyzer; it has been shown to reflect tissue oxygenation of a segment of heated skin.[9,10] A period of 15 to 20 minutes was allowed for equilibration. The sensor was moved every four hours to avoid skin irritation and burn.

Protocol

Shortly after admission to the ED, the patients were evaluated for circulatory instability, that is, hypotension, tachycardia, altered mental status, cold wet skin, and pallor. As soon as circulatory problems were recognized or suspected, the bioimpedance electrodes, pulse oximeter, and $PtcO_2$ sensors were attached, and measurements of each were observed and recorded. Pulmonary artery catheters were placed when indicated for clinical reasons, and corresponding estimations were observed, recorded, and subsequently analyzed.

Primary fluids such as albumin or hetastarch were administered for the resuscitation of circulatory deficiencies; colloids were given to expand the intravascular space without inappropriately expanding interstitial fluid.[11] On occasion, inotropes were used, when it was appropriate to avoid fluid overload. Indications for therapy were a mean arterial pressure of less than 80 mm of mercury, a cardiac index of less than 3 liters per minute per meter squared, a $PtcO_2$ of less than 60 mm of mercury with the patient breathing room air, oxygen delivery of less than 450 ml per minute per meter squared, and oxygen consumption of less than 120 ml per minute per meter squared. The therapeutic goal was to optimize the cardiac function, pulmonary function, and tissue perfusion.

Measurements were made at frequent intervals during periods of resuscitation and changes of clinical findings. After the initial resuscitation, measurements were made when the patients were resting, free of signs of anxiety, and in relatively stable clinical condition. Measurements were made before the initiation of therapeutic interventions and at various periods throughout a patient's course.

Statistical Analysis

Data from variables collected sequentially were compared using a one-way analysis of variance and the Newman-Keuls test. Linear regression analysis was used to compare the two methods of measuring cardiac output. Statistical comparisons between data obtained under different conditions were evaluated using the two-tailed Student's t test for paired distributions. Differences were considered significant at probability values of less than .05.

Results

Comparison of Cardiac Index Estimated by Thermodilution and Bioimpedance

Figure 1 compares 50 paired values of simultaneously measured cardiac index by invasive thermodilution catheters with that obtained by the noninvasive bioimpedance system. Cardiac index values varied from 2 to 5 liters per minute per meter squared. The regression equation was $Y = 0.47x + 14$ ($r^2 = 0.68$; $P < .001$). This was not as close a correlation as for a larger series of patients in an intensive care unit[8] but was considered adequate for initial physiologic analysis in the ED.

Temporal Hemodynamic and Oxygen Transport Patterns After Stroke

The temporal patterns of hemodynamic and oxygen transport events are summarized in Table 1 beginning at the time of admission to the ED. Figure 2 compares the temporal patterns of survivors and nonsurvivors for mean arterial pressure, heart rate, cardiac index, $PtcO_2$, pulse oximetry (SaO_2), oxygen delivery, oxygen consumption (VO_2), and pulmonary venous admixture. In general, the survivors had higher values for mean arterial pressure, cardiac index, $PtcO_2$, SaO_2, oxygen delivery, and VO_2 than the nonsurvivors at comparable times after admission. The heart rate and pulmonary venous mixture were higher in those who died.

Hemodynamic Patterns Before and After Nadirs

Because the lowest value (nadir) of the various hemodynamic variables occurred at different times, the temporal patterns may be out of phase and indistinct. Figure 3 shows the survivors' and nonsurvivors' temporal patterns for pulmonary arterial wedge pressure, mean arterial pressure, cardiac index, $PtcO_2$, VO_2, and oxygen delivery when the data of each variable are aligned in

TABLE 1.—*Temporal Hemodynamic and Oxygen Transport Patterns in 17 Patients With Stroke*[*]

	Hours After Admission					
Variable	0–4	4–8	8–12	12–16	16–24	24–48
CItd, liters·min^{-1}·m^{-2}	2.69±0.80	2.64±0.72	3.13±0.93	4.19±2.34	3.45±1.19	2.90±1.19
MAP, mm of mercury	77±31	90±7	98±19	85±16	85±26	90±30
PAOP, mm of mercury	10±3	9±1	11±4	7±2	11±6	14±5
CVP, mm of mercury	4±2	4±3	5±0	4±1	9±6	13±6
Heart rate, bpm	95±30	111±37	93±8	103±22	116±19	104±24
PO_2, %	95±5	98±4	99±1	98±1	91±10	95±6
$PtcO_2$, mm of mercury	111±89	98±29	88±36	97±19	97±26	74±58
$PtcCO_2$, mm of mercury	58±13	43±7	42±9	45±9	52±11	48±12
PaO_2, torr	147±105	207±47	210±34	154±50	96±49	113±59
O_2 delivery, ml·min^{-1}·m^{-2}	355±107	367±56	470±19	528±248	466±161	389±188
$\dot{V}O_2$, ml·min^{-1}·m^{-2}	145±26	123±14	87±28	77±2	146±54	122±57

CItd = cardiac index (thermodilution), MAP = mean arterial pressure, PAOP = pulmonary artery occlusion pressure, CVP = central venous pressure, bpm = beats per minute, PO_2 = partial arterial pressure of oxygen, $PtcO_2$ = partial pressure of transcutaneous oxygen, $PtcCO_2$ = partial pressure of transcutaneous carbon dioxide, O_2 = oxygen, $\dot{V}O_2$ = oxygen consumption

[*]Values are given as the mean±SD.

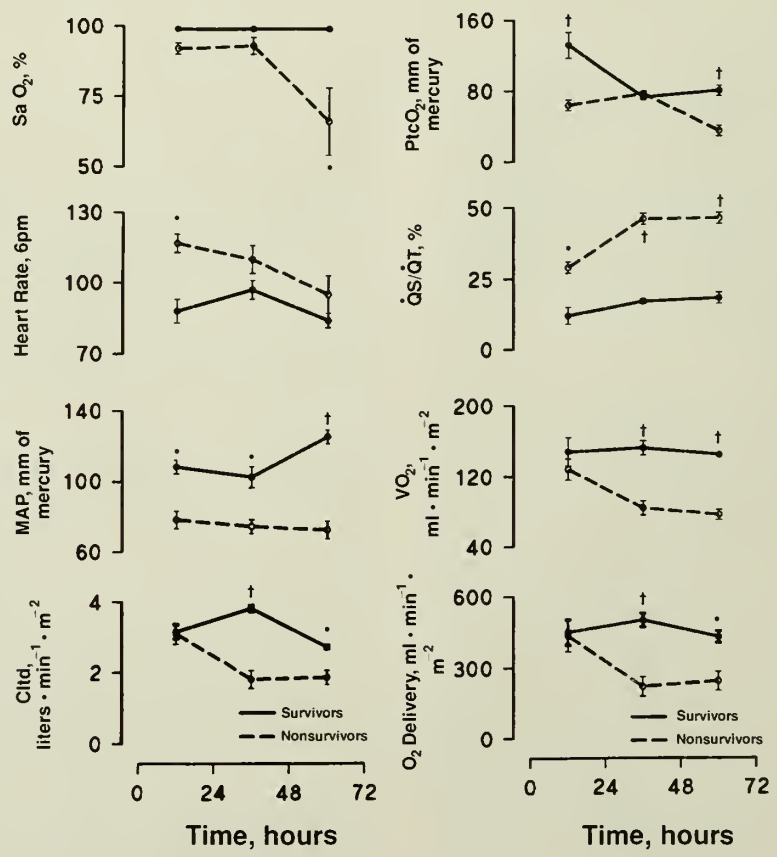


Figure 2.—Arterial hemoglobin oxygen saturation (SaO2), heart rate, mean arterial pressure (MAP), cardiac index by thermodilution (CItd), transcutaneous oxygen tension (PtcO2), pulmonary venous admixture or shunt (QS/QT), oxygen consumption (VO2), and oxygen (O2)delivery are shown in survivors and nonsurvivors during the first, second, and third days after admission to the emergency department. Note the nonsurvivors' significant decrease in SaO2, blood pressure, CItd, PtcO2, O2 delivery, and VO2 values ($P < .05$, indicated by the asterisk) and the significant rise in the QS/QT value ($P < .01$, indicated by the dagger). bpm = beats per minute

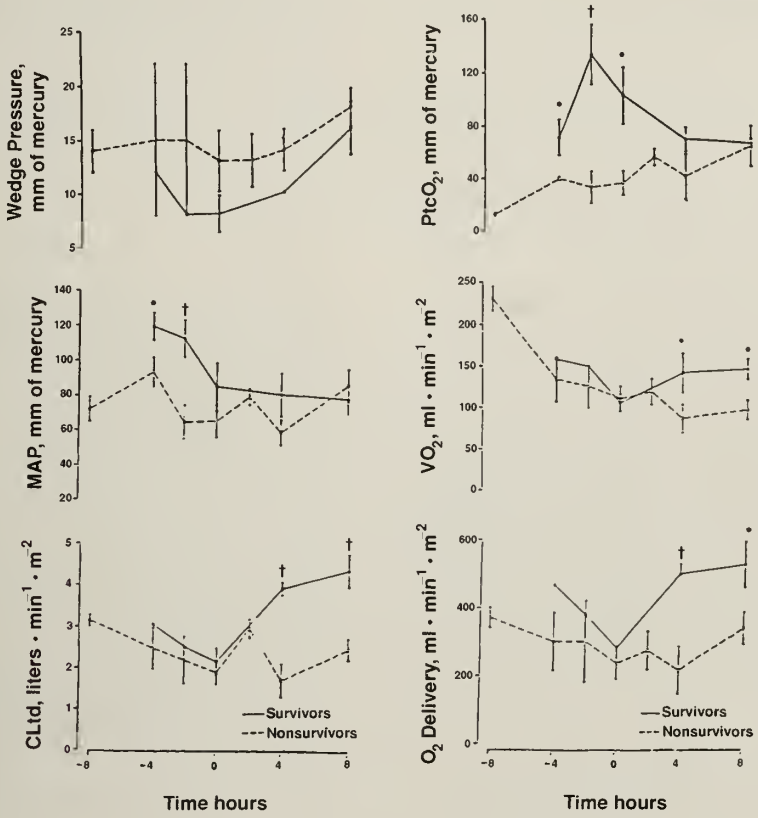


Figure 3.—Survivor and nonsurvivor patterns are shown immediately before and after the cardiac index nadir, as measured by thermodilution (CItd). Note the significant higher transcutaneous oxygen tension (PtcO2) before the nadir and the higher CItd, oxygen consumption (VO2), and oxygen (O2) delivery after the nadir (both P < .01, indicated by the dagger). MAP = mean arterial pressure, asterisk = P < .05

time before and after the cardiac index nadir. The survivors' values were generally higher in all monitored variables except the pulmonary wedge pressure.

Invasive Monitoring of Cardiac Index, Oxygen Delivery, and VO_2

Table 2 summarizes the cardiac index, oxygen delivery, and VO_2 index for survivors and nonsurvivors of stroke obtained by invasive pulmonary artery catheter placement shortly after admission to the ED. In general, the survivors had higher values in these variables.

Discussion

The primary injury that occurs in the brain tissue of patients with acute stroke is usually irreversible, but the associated circulatory dysfunction may contribute to further deterioration of cerebral function.[12] The traditional methods of monitoring, such as recording the arterial blood pressure, heart rate, and respiratory rate, are not well correlated with blood flow, SaO_2, or tissue perfusion as reflected by the cardiac index, pulse oximetry, or transcutaneous oximetry, respectively.[13] This emphasizes the inadequacy of the vital signs to reflect the more important circulatory functions that include blood flow, arterial oxygenation, and tissue perfusion. The pulmonary artery catheter is considered to be the state-of-the-art tool for precise hemodynamic monitoring. Its placement and use are personnel-intensive, costly, and time-consuming, however, and are associated with complications and logistic problems. The data are retrieved in an operator-dependent and discontinuous manner.

TABLE 2.—*Cardiac Index by Thermodilution (Citd), Oxygen Delivery, Oxygen Consumption ($\dot{V}O_2$), and Transcutaneous Oximetry ($PtcO_2$) Values Shortly After Hospital Admission in Survivors Compared With Nonsurvivors*[*]

	Hemodynamics			
Patients	*CItd, liters·min⁻¹·m⁻²*	*$PtcO_2$, torr*	*O_2 Delivery, ml·min⁻¹·m⁻²*	*$\dot{V}O_2$, mlmin⁻¹·m⁻²*
Survivors	3.44±0.82	97±58	488±127	146±38
Nonsurvivors	2.64±1.33	61±55	336±181	105±47

[*]Values are given as the mean±SD.

The availability of a new thoracic electrical bioimpedance system allows the monitoring of cardiac output in a noninvasive, continuous on-line, real-time mode.[5–8] The electrodes can be applied immediately on admission to the ED almost as easily as ECG electrodes. Monitoring can be started as soon as a patient is admitted to the ED. Several limitations with this new bioimpedance device include low signal:noise ratios from pleural effusions, chest tubes, pulmonary edema, severe congestive heart failure, and severe pneumonia.[3]

In this series, the correlation of the bioimpedance method with the thermodilution method was somewhat less accurate than in a larger series of critically ill patients, previously reported.[8] In the face, however, of exigencies surrounding the emergency admission of patients with stroke and neurologic failure, the comparison was considered satisfactory. Far more important than isolated values are trends. By a method that offers continuous hemodynamic monitoring, the temporary patterns of circulatory insufficiency can be better understood, and therapy can be started promptly.

This study represents a new approach to the hemodynamic evaluation of patients with stroke on admission to the ED. Both invasive and noninvasive data show reduced cardiac output and poor tissue perfusion at the early stages after acute stroke. Survivors demonstrated better hemodynamic variables than nonsurvivors early after admission. Whether this is the determinant or just a marker of the final outcome remains to be studied. Although optimal supranormal values have been shown to increase survival in certain groups,[14,15] the applicability of these values in stroke patients was not examined in the present series. It would be reasonable to assume, however, that identifying and correcting circulatory deficits early may result in an improved outcome.

Conclusion

Noninvasive monitoring in the immediate postadmission period allows the temporal circulatory patterns in patients with stroke and neurologic failure to be described. Data obtained by invasive and noninvasive methods show an early reduction in hemodynamic and oxygen transport variables, particularly in the nonsurvivors. In general, the survivors' mean arterial pressure, cardiac index, $PtcO_2$, oxygen delivery, and VO_2 patterns are higher than those of the patients who die after stroke. Further investigation of noninvasive methods for monitoring hemodynamic and oxygen transport data is warranted.

REFERENCES

1. Wo CCJ, Shoemaker WC, Appel PL, Bishop MH, Kram HB, Hardin E. Unreliability of blood pressure and heart rate to evaluate cardiac output in emergency resuscitation and critical illness. Crit Care Med 1993; 21:218–223

2. Bland RD, Shoemaker WC, Shabot MM. Physiologic monitoring goals for the critically ill patient. Surg Obstet Gynecol 1978; 147:833–837

3. Wo CCJ, Shoemaker WC, Bishop MH, Wang X, Patil RS, Thangaturai D. Noninvasive estimations of cardiac output and circulatory dynamics in critically ill patients. Curr Opin Crit Care 1995; 1:211–218

4. Handelsman H. Measuring cardiac output by electrical bioimpedance. In: Public Health Service Reassessment. Washington (DC): US Public Health Service; 1992, pp 1–13

5. Wang X, Sun HH, Adamson D. An impedance cardiography system: a new design. Ann Biomed Eng 1989; 17:535–565

6. Wang X, Van de Water JM, Sun HH. Hemodynamic monitoring by impedance cardiography with an improved signal processing technique. Proc IEEE Eng Med Biol 1993; 15:699–700

7. Wang X, Sun HH, Van de Water JM: Time frequency distribution technique in biological signal processing. Biomed Instrum Technol 1995; 18:203–212

8. Shoemaker WC, Wo CCJ, Bishop MH, Appel PL, Van de Water JM, Harrington GR, et al. Multicenter trial of a new thoracic electrical bioimpedance device for cardiac output estimation. Crit Care Med 1994; 22:1907–1912

9. Tremper KK, Waxman K, Shoemaker WC. Effects of hypoxia and shock on transcutaneous PO_2 values in dogs. Crit Care Med 1979; 7:526–531

10. Tremper KK, Waxman K, Bowman R, Shoemaker WC. Continuous transcutaneous oxygen monitoring during respiratory failure, cardiac decompensation, cardiac arrest, and CPR. Crit Care Med 1980; 8:377–380

11. Hauser CJ, Shoemaker WC, Turpin I, Goldberg SJ. Oxygen transport responses to colloids and crystalloids in critically ill surgical patients. Surg Gynecol Obstet 1980; 150:811–818

12. Sila CA. Prophylaxis and treatment of stroke—The state of the art in 1993. Drugs 1993; 45:329–337

13. Bishop MH, Shoemaker WC, Appel PL, Wo CC, Zwick C, Kram HB, et al. Relationship between supranormal circulatory values, time delays, and outcome in severely traumatized patientsInfluence of time and optimal resuscitation in high-risk trauma. Crit Care Med 1993; 21:56–63

14. Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee TS. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. Chest 1988; 94:1176–1186

15. Tuchschmidt J, Fried J, Astiz M, Rackow E. Elevation of cardiac output and oxygen delivery improves outcome in septic shockSupranormal oxygen delivery improves mortality in septic shock patients. Chest 1992; 102:216–220

Conferences and Reviews

Role of Clinicians in Cigarette Smoking Prevention

ELISEO J. PÉREZ-STABLE, MD, *and* ELENA FUENTES-AFFLICK, MD, MPH, *San Francisco, California*

This review is based on a talk presented at the annual meeting of the Western Association of Physicians in Carmel, California, on February 5, 1997.

Despite a gradual decrease in smoking rates among adults, the proportion of youth who smoke regularly has remained stable. Among high school students in 1997, 19.9% of white, 7.2% of African American, and 10.9% of Latino youth reported smoking during at least 20 of the previous 30 days. Ethnic differences in beliefs, attitudes, and behavior about smoking have not been systematically considered in developing prevention interventions for adolescents. Effective school-based smoking-prevention interventions have been developed, but these are usually not appropriately implemented. Policy proposals and current laws that affect the marketing of tobacco to youth need to be emphasized as evidence increases that marketing by the tobacco industry targets youth and leads to more smoking. Smoking-prevention programs have been designed to involve physicians and other health care professionals in the clinical setting, but limited data exist on their efficacy. We review the guidelines for involving the clinicians who provide care to children in preventing the onset of tobacco use, counseling parents of children who smoke, and counseling adolescents who have started smoking. Finally, we summarize the future directions of smoking-prevention research and programs.

(Pérez-Stable EJ, Fuentes-Afflick E. Role of clinicians in cigarette smoking prevention. West J Med 1998; 169:23–29)

Approximately 3,000 children in the United States begin to smoke cigarettes every day, and, on average, 4.5% of adolescents take up smoking each year.[1,2] Although smoking rates for adults have declined during the past 20 years, the rates of adolescent experimentation with and becoming regular users of tobacco have not decreased.[2–4] Nearly all initiation of tobacco use occurs before 18 years of age, and by age 13 years, about 25% of children have experimented with cigarettes.[5] Thus, developing innovative and effective approaches to prevent tobacco exposure among children is a public health priority.[6–8]

In this article, we review the current epidemiology of tobacco use by youth and examine its relationship to tobacco use among adult patterns by sex and ethnicity. Interventions to prevent tobacco use among youth have largely been focused on school-based interventions. Recently, legislated policy changes limiting access to tobacco and enforcing penalties for the sale of tobacco to minors are increasing at state and community levels. We review the role of clinicians who provide care to children in preventing the onset of tobacco use, counseling parents of children who smoke, and counseling adolescents who have started smoking. Finally, we describe future directions for programs and research in smoking prevention.

Epidemiology of Tobacco Use Among Youth

Despite a gradual decrease in cigarette smoking rates among adults during the past 30 years, little progress has been made since 1980 in reducing adolescent smoking. Among adults, smoking rates have fallen for men and women and among non-Latino whites (henceforth whites), African Americans, and Latinos.[3] Although the onset of tobacco use among young adults (aged 18–24 years) is now less frequent, most smoking initiation now takes place during adolescence. There has been a shift in the age of onset and not a decrease in smoking prevalence among youth. For example, the 1997 Youth Risk Behavior Survey showed overall smoking rates for females and males, respectively, of 69.3% and 70.9% for lifetime cigarette use 34.7% and 37.7% for current cigarette use (defined as ≥1 days in the previous month), and 15.7% and 17.6% for frequent use (defined as ≥20 days in the previous month).[9] Table 1 shows the rates for lifetime, current, and frequent

From the Division of General Internal Medicine, Department of Medicine (Dr Pérez-Stable), the Departments of Pediatrics and of Epidemiology and Biostatistics (Dr Fuentes-Afflick), and the Medical Effectiveness Research Center for Diverse Populations, University of California San Francisco School of Medicine. This work was supported in part by grant HS077373 from the Agency for Health Care Policy and Research, Washington, D.C..

Reprint requests to Eliseo J. Pérez-Stable, MD, Medical Effectiveness Research Center for Diverse Populations, University of California San Francisco School of Medicine, 400 Parnassus Ave, Rm A-405, Box 0320, San Francisco, CA 94143-0320 (e-mail: eliseo_perez-stable@ucsfdgim.ucsf.edu).

ABBREVIATIONS USED IN TEXT

ETS = environmental tobacco smoke
NCI = National Cancer Institute

use of cigarettes by sex and ethnicity from the Youth Risk Behavior Survey in 1995 and 1997.[4,9] The failure to decrease experimentation with and regular use of tobacco among youth mandates the development of effective interventions to prevent the initiation of tobacco use.

An evaluation of adolescent smoking behavior by race and ethnicity is important for anticipating adult smoking behavior in the future. The observed smoking behavior differences among adults by ethnicity indicates that this will be a fruitful focus of research. Latina and Asian adult women have substantially lower smoking rates on average than white and African American women, although there are fewer ethnic differences among men.[10] The process of acculturation or integration into mainstream US culture appears to be associated with higher smoking rates among Latina and Asian women, and over time, the female advantage in smoking rates may be reduced.[11,12]

Although an unexplained decrease in smoking occurred among African American youth from 15.7% in 1980 to 4.4% in 1993, the 1997 Youth Risk Behavior Survey reported a recent increase to 7.2%.[3,9] Virtually no change has occurred among white youth in the same period (21.8% in 1980, 22.9% in 1993, and 19.9% in 1997).[3,9] Data from national and regional surveys indicate that the frequent use of cigarettes among Latino youth has remained about 10% for the past decade (10.9% in 1997).[9] The stable smoking rates among Latino youth are concerning because of the expectedly adverse influence of acculturation over time. The lower smoking rates among Latinos and African American youth are supported by a validation study from New York.[13] No national longitudinal data exist on smoking behavior among Asian and Pacific Islander adolescents.

Predictors of Cigarette Smoking

Information on those factors that predict the onset of cigarette smoking among youth are limited. As many as three quarters of adolescents try cigarettes at least once, and about half of adolescents who try cigarettes experiment on a regular basis, defined as smoking at least once per month. Only about 20% of youth become regular daily smokers by age 18 years, however, and there are substantial ethnic differences in rates.[2] Epidemiologic data and social psychological models imply that smoking is not an "on-off" phenomenon among youth but that a continuum exists and that there is movement along the "trying," "experimenting," and "regular use" spectrum. Studies of adolescents in California suggest that "smoking susceptibility" is an important attitude that identifies youth at risk for becoming regular smokers in the future.[14] An assessment of smoking susceptibility is based on asking a respondent how certain he or she is about smoking or not smoking in the future. Thus, in designing and implementing interventions to prevent smoking, youth who are uncertain about future tobacco use need to be targeted.[14] Receptivity to tobacco advertising and the use of promotional items, however, were found to be associated with increased susceptibility to smoke and the onset of smoking experimentation in a cohort of California adolescents.[15]

Landrine and colleagues examined a diverse sample of ninth-grade youth in Los Angeles and San Diego, California, public school districts and found important ethnic differences in predictors of cigarette smoking.[16] In this cross-sectional study of 4,375 students from four ethnic groups, the researchers used multivariate models to examine all of the psychosocial and behavioral factors that had been associated with the onset of tobacco use. Peer smoking, defined by "how many of your ten closest friends smoke" and peer pressure from modeling, was the most important predictor of smoking among white youth; a lower grade-point average was the second most important predictor. Among African Americans, on the other hand, a greater risk-taking attitude was the predominant predictor of smoking, whereas peer smoking and grade-point average were not significant.

Among the Latino youth in the study, peer smoking was the most important predictor, although it explained less of the variance than among whites, and a higher level of depressive symptoms was the second most important predictor.[16] The level of acculturation also influenced predictors of smoking among Latinos, with days absent

TABLE 1.—*Tobacco Use in High School Students, by Sex and Ethnicity, Youth Risk Behavior Study, 1995 and 1997, %**

	White				*African American*				*Latina*			
	1995		*1997*		*1995*		*1997*		*1995*		*1997*	
Tobacco Use	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*
Lifetime use or ever tried	71	71	70	70	71	63	70	67	78	75	77	73
Current use (≥1 of 30 days)	37	40	40	40	28	12	28	17	35	33	36	32
Frequent use (≥20 of 30 days)	18	21	20	20	9	1	10	4	11	9	13	8
Smokeless use (chew of snuff, ≥1 of 30 days)	25	3	21	2	4	1	3	1	6	3	8	1

*Adapted from Centers for Disease Control and Prevention.[4,9]

from school being significant among the less acculturated. Among the most acculturated youth, risk-taking attitude and depressive symptoms were significant predictors, and among the bicultural Latinos, risk-taking attitude and grade-point average were also significant predictors. The most significant predictors of smoking among Asians were days absent from school, peer smoking, and alcohol consumption by adult role models.[16] The striking findings of this study were the absence of a significant association between parental smoking and youth smoking and the nearly universal importance of peer smoking (except among African Americans). These observations can be used to develop interventions.

There is a clear need for additional basic social and behavioral research of adolescents of all ethnic groups to further understand the factors that influence smoking experimentation, initiation, regular use of cigarettes, and frequent use leading to dependence. Nicotine dependence may develop as a result of biologic susceptibility in the appropriate social environment. Thus, multidisciplinary collaboration among scientists is needed to further identify those factors that lead youth to become addicted to nicotine.

Health Consequences of Tobacco Use in Adolescents

Active occasional smoking by adolescents leads to nicotine addiction, with subsequent increased morbidity and mortality from cancer and cardiovascular disease. Projections from the Centers for Disease Control and Prevention, based on current smoking rates among young adults, show that 885,000 persons currently 17 years of age or younger and living in seven western states will die of causes directly attributable to nicotine addiction.[17]

More short-term adverse health consequences of cigarette smoking are also evident among young people who smoke. Cigarette smoking among adolescents causes an increase in respiratory tract infections, including the common cold, and an overall increase in respiratory symptoms.[2,18] Subtle but quantifiable changes in pulmonary function, exacerbation of asthma, and decreased physical fitness are also established consequences of cigarette smoking among adolescents.[2,18] Young women who smoke while pregnant will have smaller infants, are at an increased risk of having infants with congenital malformations, and a greater likelihood of having spontaneous abortions.[2] Cigarette smoking also functions as a "gateway drug," leading to an increased likelihood that youth will use other substances, including alcohol and illicit drugs, with their subsequent social sequelae.[2]

Smoking Prevention in Schools

Many controlled trials have evaluated the efficacy of school-based interventions to prevent cigarette smoking initiation and regular use.[2] A meta-analysis of 90 school-based programs indicated that there is a 4.5% lower prevalence of regular cigarette use among youth in the social influence intervention programs.[19] Although the incidence and prevalence of cigarette smoking were significantly reduced in adolescents for as long as four years, follow-up to six years failed to show significant differences between control and intervention groups.[19,20] Observed ethnic differences in smoking attitudes, beliefs, and behavior have not been systematically incorporated into a prevention intervention directed at youth of diverse backgrounds. Despite the apparent failure at sustaining decreased smoking rates in long-term follow-up, the content of effective interventions has been well defined.

The most successful school-based smoking-prevention programs emphasize the social factors that influence smoking and the short-term consequences of smoking and teach adolescents skills on how to resist social pressures or develop refusal skills that can be applied to smoking or other issues.[2] Furthermore, school-based smoking-prevention programs need to be incorporated into the existing curricula, involve students in the delivery, be led by specially trained teachers, and incorporate culturally appropriate content. Unfortunately, most school-based smoking-prevention curricula are not set up with these components in mind, are presented as special add-on programs in one or two classes, are taught by a teacher who has received no special training on the topic, and are frequently focused on the rational approach of providing information, which is usually ineffective.[2] Furthermore, to maximize the limited efficacy of the school-based programs, these need to be implemented in the sixth grade or earlier and include at least five sessions during the course of a school year. Considering that most school districts have limited programs, the implementation of adequately funded, universal school-based smoking-prevention programs starting in the sixth grade could have a favorable effect on adult smoking rates in just a few years.

Health Policy Interventions

Advocating policy changes and enforcing existing laws that prohibit the sale of tobacco products to youth are strategies to decrease access to tobacco among children that have been actively pursued by the tobacco control community in recent years. Increasing the cost of cigarettes by taxation not only helps finance tobacco education but also decreases access to tobacco by youth. The real price of a pack of cigarettes as a proportion of the real weekly income of high school seniors, however, was only 1.9% in 1989, which is only a slight increase from 1.4% in 1982.[21] Cigarettes remained relatively inexpensive to most adolescents at average 1989 prices, although increased state taxes since that time have increased the price. Laws in most states that require vendors to document the age of buyers as 18 years of age or older are often not enforced. Data from the Youth Risk Behavior Survey in 1995 showed that about half of 12th graders who smoked at least 1 of the previous 30 days purchased cigarettes on their own, and 70% of males and 86% of females who did so were not asked for proof of age.[4]

Although the proportion of adolescents who purchased cigarettes on their own varied somewhat by age, sex, and ethnicity, overall 75% of males and 81% of females who purchased cigarettes were not asked to show proof of age when purchasing cigarettes.[4] Enforcement of these ordinances would probably decrease easy access to tobacco and affect the number of young people becoming addicted to nicotine.

The tobacco industry increased annual expenditures from $2.1 billion in 1980 to $4.2 billion in 1989 (in 1993 dollars) to promote their product. Promotional expenditures account for the entire increase over this time because direct advertisement expenditures have actually decreased from $1.3 billion to about $1 billion.[21] Among persons aged 12 to 17 years, 25% of nonsmokers report having received promotional items from tobacco companies, which are often obtained at sporting and cultural events.[2] This increased tobacco industry investment in marketing expenditures parallels increased initiation rates among adolescents during the same period, and it has been shown that adolescents smoke the most heavily advertised brands.[21,22] The causal association of receptivity and exposure to tobacco industry promotional items and advertisements is increasing.[15,23] The successful advertisement logos of the tobacco industry are well-recognized symbols by adults, adolescents, and children, and in fact, 6-year-old children in one study were as likely to identify the "Joe Camel" cartoon figure as they were Mickey Mouse.[24]

The federal government is considering implementing new regulations on the tobacco industry, using the fact that nicotine is a drug and cigarettes are a drug delivery system. This has been linked to recent revelations by one cigarette manufacturer that undermine the industry's legal defense from litigation by former smokers in whom cancer and other diseases develop. One proposal suggested that the Food and Drug Administration regulate the nicotine content of cigarettes by gradually decreasing the amount per cigarette over several years.[25] Thus, cigarettes would lose the power of delivering an addictive substance, and the number of youth who become regular smokers would likely decrease significantly. By weaning the nicotine content of cigarettes, addicted smokers would also not suffer abstinence symptoms abruptly. Some form of increased regulation of the tobacco industry within the decade appears likely.

Clinician-Based Interventions

Physician- or nurse-mediated interventions to promote smoking cessation among adults were developed, implemented, and tested in randomized control designs with moderate effects on biochemically proven smoking cessation in diverse clinical settings, ranging from 5% to 15% abstinence at one year.[26–29] This strategy led to a National Cancer Institute (NCI) program to incorporate primary health care clinicians in a public health approach to smoking cessation.[28] The established effectiveness of nicotine replacement therapy in conjunction with minimal physician counseling to quit smoking has further strengthened this approach.[30]

A similar program has been developed by the NCI to target clinicians caring for children with the use of the five *As*: anticipate, ask, advise, assist, and arrange.[31] *Anticipate* refers to planning what tobacco-related risks need to be addressed during a child's development. *Ask* about experimenting with smoking starting at age 8 years, and ask parents about their smoking and other sources of environmental tobacco smoke (ETS) exposure for the child. *Advise* adolescents (and parents) to quit smoking, and *assist* with self-help literature, specific techniques, nicotine replacement therapy, or referral to groups. Finally, *arrange* for follow-up visits to reinforce quitting or to review circumstances of relapse.

Unlike with the adult literature, studies that have evaluated the effectiveness of the NCI program directed at clinicians caring for children, the usefulness of interventions focused on decreased ETS exposure, or the applicability of these methods among diverse ethnic groups are limited.[32] In a survey of residents in primary care specialties, only 32% of pediatric residents reported any training in smoking cessation counseling, and most scored significantly lower than their primary care colleagues in family medicine and general internal medicine.[33] Pediatric residents who were taught smoking-cessation counseling techniques however, performed as well as those in other primary care specialties.[34] A feasibility study showed that pediatric residents trained to use the NCI program raised tobacco issues more often, counseled adolescents about smoking cessation more frequently, and reported the use of more effective techniques than a nonrandomized comparison group who failed to attend the teaching seminars.[35]

Limited empiric evidence is available on the practice of pediatric clinicians regarding tobacco prevention. A survey of 100 practicing pediatricians in Maine showed that 91% advise parents who smoke to quit, spending an average of 4.9 minutes doing so, but only 43% talk to at least three quarters of parents about the effects of smoking on their children.[36] A similar study of 72 pediatricians in Vermont found that 29 (40%) routinely queried parents about smoking; 8 (11%) recorded the information in the medical record; and 68 (94%) advised at least some parents to quit smoking, spending an average of 4.4 minutes doing so.[37] Environmental tobacco smoke exposure was addressed by the Vermont pediatricians by advising parents to smoke away from children (55 physicians [7776%]), cutting down the consumption of cigarettes (29 physicians [40%]), and setting a quit date (16 physicians [22%]).[37] A survey of primary care physicians from Connecticut conducted in 1992 showed that only 20% of pediatricians and 24% of family physicians always counseled 10- to 12-year-old children about smoking prevention.[38] Recently, a survey of California primary care physicians caring for adolescents found that pediatricians screen 11- to 14-year-old adolescents for regular smoking 61% of the time during a routine examination, only 10% of the time during an acute care visit, and 21% of the time asked about ever having tried a cigarette.[39]

Other data collected from pediatricians and parents of their patients indicate that counseling about smoking prevention and cessation and about the harms of ETS exposure would be welcomed and considered important.[40,41] Barriers to counseling about smoking prevention or cessation reported by pediatricians include the perception that techniques are ineffective, feeling ill-at-ease about giving this advice, lack of time, and fear that parents may think that this is intrusive.[33,37,38] In one survey of parents, only 15% reported that their smoking was "none of the doctors' business," but more than half thought that talking about smoking was "part of the pediatrician's job."[41] The amount of time available to dedicate to smoking prevention and cessation for children, adolescents, and their parents may be even more limited in managed care–dominated areas such as California. Demonstrating the efficacy of clinician-based interventions would assist in prioritizing smoking prevention in the medical groups and health plans. Nurses and other office staff can provide much of the structural and interactive content of an office-based intervention, but primary care clinicians need to be trained in the appropriate techniques.

Preventing ETS Exposure in Children

Exposure to ETS has been associated with a substantial increase in risk of the sudden infant death syndrome, acute respiratory tract infections, recurrent otitis media with chronic middle-ear effusions, exacerbation of asthma, and admission to a hospital for bronchitis and pneumonia in children younger than 5 year.[18,42] Passive smoking was estimated to account for $661 million in medical expenditures in 1987, and maternal smoking increases the average annual health care expenditures by $175 per year per child aged 2 years and younger.[43] Some studies have found that parents' cigarette smoking teaches the utility and acceptability of smoking to their children and is strongly associated with increased smoking by their children as adults.[18,42] Environmental tobacco smoke exposure during childhood has been found to significantly increase the risk of lung cancer in adults who never actively smoke,[44,45] and among adults, ETS exposure increases the risk of morbidity and mortality from heart disease.[46] A recent study of 175 healthy Puerto Rican children used urinary cotinine levels to quantify ETS exposure and showed that smoke from their mothers made the greatest contribution to ETS, households where 20 or more cigarettes per day were smoked doubled urinary cotinine excretion in children, and children aged 2 to 4 years were significantly more exposed than children aged 5 to 11 years.[47]

In 1986, an estimated 53% to 76% of households in the United States contained one adult resident who smoked cigarettes, and as many as 12 million children 5 years of age and younger were exposed to ETS.[45] A recent national survey reported that 15 million children and adolescents younger than 18 years were exposed to ETS, with as many as half of smoking adults having children residing in their homes, and most of these homes permitted smoking in some or all areas of the home.[48] In California, 7.3% (±0.8%) of households had a current cigarette smoker and children in the home; 72.3% of those households allowed smoking in some or all areas of the home.[48] The Third National Health and Nutrition Examination Survey (1988–1991) found that 43% of children aged 2 months to 11 years lived in a home with at least one smoker.[49] Furthermore, the geometric mean of serum cotinine levels among non–tobacco users with ETS exposure was highest among children aged 4 to 11 years.[49] The California 1993 Tobacco Survey reported that 75% to 85% of households with children or adolescents were entirely smoke free, and Asian and African American households were more likely to be smoke free than white and Latino households.[14]

Several studies have examined the efficacy of clinical interventions to decrease ETS exposure in children. An intensive counseling intervention directed at families of asthmatic children (aged 6–17 years) reported a significant 79% reduction in ETS exposure (validated by nicotine air monitor) at one year in the intervention group compared with 42% for a monitored group and 34% for a "usual care" group, with sustained effects at two years.[50,51] These results with an intensive intervention in families with chronically ill children imply that behavioral change to minimize ETS exposure is feasible. A randomized trial of a home-based nurse-delivered intervention was evaluated in 933 infants, of whom 25.2% had smoking mothers.[52] Among the 121 infants of smoking mothers who completed the study, infants in the intervention group were exposed to 5.9 fewer cigarettes per day and reported a lower prevalence of persistent respiratory symptoms despite no differences in urinary cotinine excretion.[52] Wall and colleagues randomly assigned 49 pediatric practices to receive a 45-minute training intervention on brief counseling for new mothers on the first four well-baby visits to decrease ETS exposure compared with a hospital packet with written information received by all mothers.[53] Pediatricians were taught to deliver a two-minute brief intervention with an emphasis on counseling smoking mothers (42.5% of study sample) to quit. At six months' follow-up, smoking mothers in the intervention group had higher quit rates (5.9% versus 2.7%) and lower relapse rates (45% versus 55%), providing evidence that a brief intervention can have a positive effect on maternal smoking.[53]

Parents of young children visit a pediatrician more often than any other physician, and these visits offer a window of opportunity to effect a behavior change among these parents and promote smoking cessation.[36,37] Pediatric clinicians may be uniquely positioned to counsel these adults to quit smoking but need to be comfortable with delivering this intervention. Because less than half of these adults are advised to quit by their own primary physicians, a reminder system for pediatricians could increase the likelihood that time is dedicated to this important issue. Studies in adult medical practices showed that placing a reminder in the patient record increased the time that physicians spent counseling smok-

ers from 1.4 to 3.6 minutes and increased the percentage of patients who had quit successfully from 1.3% to 7.0% at one year and that setting a specific date to quit smoking increased the likelihood of a quit attempt by four to seven times.[54] The efficacy of nicotine replacement therapy for about eight weeks has been demonstrated in randomized clinical trials to increase the likelihood of abstinence at six months from 9% to 22%.[30] Recently, similar efficacy results were shown with treatment using sustained-release bupropion hydrochloride in nondepressed smokers motivated to quit (validated abstinence of 23% versus 12% at 12 months).[55] Thus, given the evidence on the feasibility and effectiveness of training clinicians to counsel their patients to quit smoking, pediatric clinicians are uniquely positioned to counsel a smoking parent to quit smoking.

Training pediatric clinicians how to counsel parents who smoke to quit is one method to decrease ETS exposure among children 5 years of age and younger. Among most parents who are nonsmokers, a pediatric clinician can also teach parents about assessing for and preventing ETS exposure. For example, a pediatric clinician may need to assist a nonsmoking parent (more often the mother) in advising a smoking parent or relative on how to quit, for the well-being of the family. The pediatrician also needs to plan for the prevention of smoking initiation by counseling parents on talking to their children about smoking at an early age and to actively counteract tobacco industry advertisements and promotions directed at children. Clinicians can also provide leadership and support to enhance school-based programs and community-based efforts. Furthermore, asking children beginning at age 8 years about experimenting with tobacco use needs to become routine practice for pediatric clinicians.

Conclusions and Future Directions

The lack of success in controlling tobacco use among US youth stands in contrast to the reasonable success among adults. If current trends continue, adolescent smoking rates will soon equal those of adults, and thus, the prospect for further reductions in national smoking rates, tobacco-related disease rates, and economic costs is unlikely to change in the foreseeable future.

A wider implementation of effective techniques used in school-based programs to prevent tobacco use among young persons is needed. Culturally appropriate interventions to prevent tobacco use need to be developed and implemented in other than school-based settings where most efforts to prevent the onset of cigarette smoking have taken place. Community-based interventions with outreach through neighborhoods and youth-oriented media, targeting youth at an early age (such as 8 years), need to be considered as viable intervention strategies.

Policy changes to decrease access of tobacco products to children by increasing their cost and making it more difficult to purchase cigarettes should be adopted at state and federal levels. Additional regulation of tobacco industry by limiting advertisement and promotion and regulating nicotine content will require a concerted federal effort and popular support to implement. Physicians and other health professionals caring for children will need to become more actively involved in promoting smoking prevention.

REFERENCES

1. Fiore MC, Novotny TE, Pierce JP, Hatziandreu EJ, Patel KM, Davis RM. Trends in cigarette smoking in the United States: the changing influence of gender and race. JAMA 1989; 261:49–55

2. Preventing tobacco use among young people: a report of the Surgeon General. Atlanta (Ga): US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 1994

3. Giovino GA, Schooley MW, Zhu BP, et al. Surveillance for selected tobacco-use behaviors—United States, 1900-1994. MMWR CDC Surveill Summ 1994; 43(SS-3):1–43

4. Kann L, Warren CW, Harris WA, et al. Youth Risk Behavior Surveillance—United States, 1995. MMWR CDC Surveill Summ 1996; 45(SS-4):1–84

5. Giovino GA, Henningfield JE, Tomar SL, Escobedo LG, Slade J. Epidemiology of tobacco use and dependence. Epidemiol Rev 1995; 17:48–65

6. Kessler DA, Notanblutt SL, Wilkenfeld JP, Mayl SL, Bernstein IBG, Thompson L. Nicotine addiction: a pediatric disease. J Pediatr 1997; 130:518–524

7. Glynn TJ, Greenwald P, Mills SM, Manley MW. Youth tobacco use in the United States—Problems, progress, goals, and potential solutions. Prev Med 1993; 22:568–575

8. Reid DJ, McNeill AD, Glynn TJ. Reducing the prevalence of smoking in youth in western countries: an international review. Tobacco Control 1995; 4:266–277

9. Office on Smoking and Health, Division of Adolescent and School Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention (CDC). Tobacco use among high school students—United States, 1997. MMWR Morb Mortal Wkly Rep 1998; 47:229–233

10. CDC. Cigarette smoking among adults—United States, 1994. MMWR Morb Mortal Wkly Rep 1996; 45:588–590

11. Marín G, Pérez-Stable EJ, Marín BV. Cigarette smoking among San Francisco Hispanics: the role of acculturation and gender. Am J Public Health 1989; 79:196–199

12. Jenkins CNH, McPhee SJ, Bird JA, Ngoc-The H, Bonilla BA, Thai VK. Cancer risks and prevention behaviors among Vietnamese refugees. West J Med 1990;153:34–39

13. Wills TA, Cleary SD. The validity of self-reports of smoking: analyses by race/ethnicity in a school sample of urban adolescents. Am J Public Health 1997; 87:56–61

14. Pierce JP, Evans N, Cavin SW, et al. Tobacco use in California: regional vs. state level changes, 1990–1993, San Francisco Region. La Jolla (Calif): University of California–San Diego; 1994

15. Pierce JP, Choi WS, Gilpin EA, Farkas AJ, Berry CC. Tobacco industry promotion of cigarettes and adolescent smoking. JAMA 1998; 279:511–515

16. Landrine H, Richardson JL, Klonoff EA, Flay B. Cultural diversity in the predictors of adolescent cigarette smoking: the relative influence of peers. J Behav Med 1994; 17:313–346

17. CDC, BRFSS Coordinators. Projected smoking-related deaths among youth—United States. MMWR Morb Mortal Wkly Rep 1996; 45:971–974

18. Gidding SJ, Morgan W, Perry C, Isabel-Jones J, Bricker JT, for Committee on Atherosclerosis and Hypertension in Children. Active and passive tobacco exposure: a serious pediatric health problem. Circulation 1994; 90:2581–2590

19. Bruvold WH. A meta-analysis of adolescent smoking prevention programs. Am J Public Health 1993; 83:872–880

20. Flay BR, Koepke D, Thompson SJ, Santi S, Best JA, Brown KS. Six-year follow-up of the first Waterloo school smoking prevention trial. Am J Public Health 1989; 79:1371–1376

21. Cummings KM, CDC. Trends in smoking initiation among adolescents and young adults—United States, 1980–1989. MMWR Morb Mortal Wkly Rep 1995; 44:521–525

22. CDC. Changes in the cigarette brand preferences of the adolescent smokers—United States, 1989–1993. MMWR Morb Mortal Wkly Rep 1994; 43:577–581

23. King C, Siegel M, Celebucki C, Connolly GN. Adolescent exposure to cigarette advertising in magazines. JAMA 1998; 279:516–520

24. DiFranza JR. Who profits from tobacco sales to children? JAMA 1990; 263:2784–2787

25. Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction: the implications of tobacco regulation. N Engl J Med 1994; 331:123–125

26. Cummings SR, Coates TJ, Richard RJ, et al. Training physicians in counseling about smoking cessation: a randomized trial of the 'Quit for Life' Program. Ann Intern Med 1989; 110:640–647

27. Cohen SJ, Stookey GK, Katz BP, Drook CA, Smith DM. Encouraging primary care physicians to help smokers quit: a randomized controlled trial. Ann Intern Med 1989; 110:648–652

28. Glynn TJ, Manley MW. How to help your patients stop smoking: a National Cancer Institute manual for physicians. Bethesda (Md): US Department of Health and Human Services, Public Health Service, National Institutes of Health, National Cancer Institute; 1989

29. Tobacco and the clinician: interventions for medical and dental practice. Washington (DC): US Department of Health and Human Services, Public Health Service, National Institutes of Health, NIH publication No. 94-3693, 1994

30. Fiore MC, Smith SS, Jorenby DB, Baker TB. The effectiveness of the nicotine patch for smoking cessation: a meta-analysis. JAMA 1994; 271:1940–1947

31. Epps RP, Manley MW. A physician's guide to preventing tobacco use during childhood and adolescence. Rockville (Md): National Cancer Institute; 1990

32. Epps RP, Manley MW, Glynn TJ. Tobacco use among adolescents: strategies for prevention. Pediatr Clin North Am 1995; 42:389–402

33. Kenney RD, Lyles MF, Turner RC, et al. Smoking cessation counseling by resident physicians in internal medicine, family practice, and pediatrics. Arch Intern Med 1988; 148:2469–2473

34. Strecher VJ, O'Malley MS, Villagra VG, et al. Can residents be trained to counsel patients about quitting smoking? Results from a randomized trial. J Gen Intern Med 1991; 6:9–17

35. Klein JD, Portilla M, Goldstein A, Leininger L. Training pediatric residents to prevent tobacco use. Pediatrics 1995; 96:326–330

36. Frankowski BL, Secker-Walker RH. Advising parents to stop smoking: opportunities and barriers in pediatric practice. AJDC 1989; 143:1091–1094

37. Frankowski BL, Weaver SO, Secker-Walker RH. Advising parents to stop smoking: pediatricians and parents attitudes. Pediatrics 1993; 91:296–300

38. Gregorio DI. Counseling adolescents for smoking prevention: a survey of primary care physicians and dentists. Am J Public Health 1994; 84:1151–1153

39. Franzgrote M, Ellen JM, Millstein SG, Irwin CE. Screening for adolescent smoking: results of a survey of primary care physicians in California. Am J Public Health 1997 Aug;87(8):1341-1345

40. Cheng TL, Savageau JA, Bigelow C, Charney E, Kumar S, DeWitt TG. Assessing mothers' attitudes about physician's role in child health promotion. Am J Public Health 1996; 86:1809–1812

41. Frankowski BL, Secker-Walker RH. Pediatricians' role in smoking prevention and cessation. In: Institute NC, editor. Tobacco and the clinician: interventions for medical and dental practice. Washington (DC): US Department of Health and Human Services, Public Health Service, National Institutes of Health; 1994, pp 232–245. NIH publication No. 94-3693

42. The health consequences of involuntary smoking: a report of the Surgeon General. Washington (DC): US Department of Health and Human Services, Public Health Service, Office of the Assistant Secretary for Health, Office on Smoking and Health; 1986. DHHS publication No. (CDC) 87-8398

43. Stoddard JJ, Gray B. Maternal smoking and medical expenditures for childhood respiratory illness. Am J Public Health 1997; 87:205–209

44. Janerich JT, Thompson WD, Varela LR, et al. Lung cancer and exposure to tobacco smoke in the household. N Engl J Med 1990; 323:632–636

45. US Environmental Protection Agency, Office of Research and Development, Office of Air and Radiation. Respiratory health effects of passive smoking: lung cancer and other disorders. Washington (DC): US Department of Health and Human Services, Public Health Service, National Institutes of Health; 1993

46. Glantz SA, Parmley WW. Passive smoking and heart disease. Circulation 1991; 83:1–12

47. Preston AM, Ramos LJ, Calderon C, Sahai H. Exposure of Puerto Rican children to environmental tobacco smoke. Prev Med 1997; 26:1–7

48. CDC. State-specific prevalence of cigarette smoking among adults, and children's and adolescents' exposure to environmental tobacco smoke—United States, 1996. MMWR Morb Mortal Wkly Rep 1997; 46:1038–1043

49. Pirkle JL, Flegal KM, Bernert JT, Brody DJ, Etzel RA, Maurer KR. Exposure to the U.S. population to environmental tobacco smoke: the third National Health and Nutrition Examination Survey, 1988 to 1991. JAMA 1996; 275:1233–1240

50. Wahlgren DR, Hovell MF, Meltzer SB, Hofstetter CR, Zakarian JM. Reduction of environmental tobacco smoke exposure in asthmatic children: a 2-year follow-up. Chest 1997; 111:81–88

51. Hovell MF, Meltzer SB, Zakarian JM, et al. Reduction of environmental tobacco smoke exposure among asthmatic children: a controlled trial. Chest 1994; 106:440–446

52. Greenberg RA, Stretcher VJ, Bauman KE, et al. Evaluation of a home-based intervention program to reduce infant passive smoking and lower respiratory illness. J Behav Med 1994; 17:273–290

53. Wall MA, Severson HH, Andrews JA, Lichtenstein E, Zoref L. Pediatric office based smoking intervention: impact on maternal smoking and relapse. Pediatrics 1995; 96:622–628

54. Kottke TE, Battista RN, DeFriese GH, Brekke ML. Attributes of successful smoking cessation interventions in medical practice. JAMA 1988; 259:2883–2889

55. Hurt RD, Sachs DPL, Glover ED, et al. A comparison of sustained-release bupropion and placebo for smoking cessation. N Engl J Med 1997; 337:1195–1202

Conferences and Reviews

Excimer Laser Refractive Surgery

EDWARD E. MANCHE, MD, *Stanford, California*; JONATHAN D. CARR, MD, *Atlanta, Georgia*; WELDON W. HAW, MD, *Stanford, California*; *and* PETER S. HERSH, MD, *Newark, New Jersey*

Review stimulated by publication of the epitome Photoreactive Keratectomy, *(McDonnell PJ, The Western Journal of Medecine, February 1997;166:139–140)*

Excimer laser photorefractive keratectomy and excimer laser in situ keratomileusis are relatively new treatment modalities that can be used to correct refractive errors of the eye. They are most commonly used to correct myopia (nearsightedness) but can also be used to correct hyperopia (farsightedness) and astigmatism. The excimer laser alters the refractive state of the eye by removing tissue from the anterior cornea through a process known as photoablative decomposition. This process uses ultraviolet energy from the excimer laser to disrupt chemical bonds in the cornea without causing any thermal damage to surrounding tissue. The modified anterior corneal surface enables light to be focused on the retina, thereby reducing or eliminating the dependence on glasses and contact lenses. We discuss in detail all aspects of excimer laser refractive surgery—techniques, indications and contraindications, clinical outcomes, and complications.

(Manche EE, Carr JD, Haw WW, Hersh PS. Excimer laser refractive surgery. West J Med 1998; 169:30–38)

Substantial refractive errors are present in nearly 50% of the US population. Refractive errors cause objects of regard to be focused either in front of or behind the retina and result in blurred vision. These refractive errors are typically corrected with either glasses or contact lenses. About 25% of the population is nearsighted (myopic), and about 20% is farsighted (hyperopic).[1] Most of the population has no substantial refractive error (emmetropic). About 30% of eyes with refractive errors also have some degree of astigmatism.[1]

In myopia, the optical power of a resting (unaccommodating) eye is too strong, and the light rays from a distant object are focused to a point in front of the retina (Figure 1). In hyperopia, the optical power of a resting (unaccommodating) eye is too weak, and the light rays from a distant object are focused to a point behind the retina (Figure 2). In emmetropia, the optical power of a resting (unaccommodating) eye is perfect, and the light rays from a distant object are focused directly onto the retina (Figure 3). In eyes with astigmatism, the situation is slightly more complex. In astigmatism, the anterior refracting surface of the eye is slightly elliptical rather than spherical. This causes light rays from a distant object to come into focus at two discrete points in the eye (Figure 4).

Currently, two types of excimer laser surgery are being used to reshape the cornea and thereby change the refractive power of the eye. The first procedure is photorefractive keratectomy (PRK), which involves the use of an excimer laser to reshape the anterior corneal surface.[2] The PRK procedure is commonly used to correct myopia and astigmatism. Outside the United States, PRK has also been used to correct hyperopia, and clinical trials are currently underway in the United States. In laser in situ keratomileusis (LASIK), the excimer laser is used to reshape the cornea under a corneal flap. In this review, we discuss in detail all aspects of excimer laser refractive surgery, including techniques, indications, contraindications, clinical outcomes, and complications.

Excimer Laser Principles

The excimer laser is based on the combination of two gases: a noble gas and halogen. These gases are stable in their normal low-energy state. When a high-voltage electrical discharge is delivered in a laser cavity containing these gases, however, the gases combine to form a higher-energy excited–gas state compound. The term "excimer" is derived from a contraction of "excited dimer." On the

From the Departments of Ophthalmology, Stanford University School of Medicine, Stanford, California (Drs Manche and Haw); Emory University School of Medicine, Atlanta, Georgia (Dr Carr); and the University of Medicine and Dentistry of New Jersey–New Jersey Medical School, Newark, New Jersey (Dr Hersh).

Reprint requests to Edward E. Manche, MD, Department of Ophthalmology, Stanford University School of Medicine, 300 Pasteur Dr, Rm A157, Stanford, CA 94305-5308.

ABBREVIATIONS USED IN TEXT

D = diopters
LASIK = laser in situ keratomileusis
PRK = photorefractive keratectomy

dissociation of this high-energy compound, a photon of energy is released that corresponds to the bond energy of the noble gas-halogen molecule. This wavelength of light energy is amplified in the laser system and results in the production of a high-energy discrete pulse of laser energy. The specific wavelength of an excimer laser depends on the composition of the gases used in the laser system. The current excimer laser systems use argon and fluorine gases. The argon-fluorine excimer lasers emit energy at a wavelength of 193 nm. This wavelength falls in the UV-C range of the light spectrum. In contrast, the krypton-fluoride excimer laser used in early laboratory studies emits a wavelength of 248 nm.[3,4]

The 193-nm excimer laser energy is well absorbed by the proteins, glycosaminoglycans, and nucleic acids that make up the cornea. Because a 193-nm photon is of higher energy than the molecular bond strength of these compounds, absorption of the laser energy results in a breaking of the bonds. The molecular fragments that thus result are ejected from the surface of the cornea at supersonic speeds. The excimer laser tissue removal process is termed "ablative photodecomposition," and it involves the removal of tissue from the corneal surface, rather than cutting tissue like a scalpel. When this procedure is used clinically, the ablated tissue appears as an effluent plume. Analysis of this plume has shown it to comprise a variety of high-molecular-weight hydrocarbons.[5]

Currently approved lasers have beam diameters of 6.0 to 6.5 mm. Wherever this broad beam impinges on tissue, molecular bonds will be broken and tissue removed. Hence, relatively large areas of the cornea can be treated with each pulse. The excimer laser technique is, thus, qualitatively different from refractive surgical techniques such as radial keratotomy, which achieves corneal reshaping through biomechanical changes mediated through thin knife incisions.

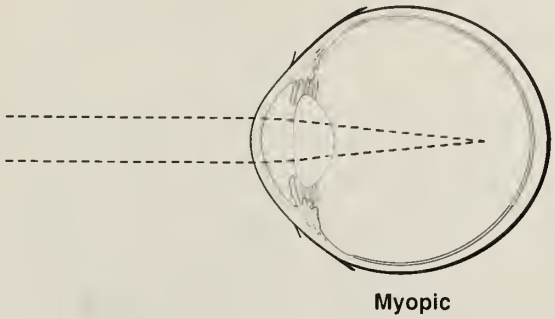


Figure 1.—The ray diagram of a myopic eye shows that the refracting power of the eye is too strong. The light rays from a distant object focus to a point in front of the retina.

Several attributes of the argon-fluoride excimer laser ablation make it particularly appropriate for corneal sculpting. The laser energy is well absorbed near the corneal surface and, thus, should have few deep direct or secondary mechanical (shock-wave) effects on the corneal tissue. The ablation process is rapid, and excess energy is ejected with the effluent plume.[6] There is minimal thermal damage to the surrounding tissue. Because of these qualities, the 193-nm excimer laser can be used to meticulously reshape large areas of the corneal surface while minimizing damage to remaining tissue.[4]

Although apparently relatively little "collateral" damage occurs to the corneal tissue with excimer laser treatment, corneal wound healing remains a major variable affecting clinical outcomes. Corneal wound healing includes epithelial healing over the ablated area[7] and new collagen synthesis in the superficial stroma in the area of photoablation.[8] Such wound healing likely accounts for between-patient variation in treatment results. The corneal wound healing that does occur appears to result in acceptable clinical outcomes.

There is concern about the potential for mutagenesis or carcinogenesis with any laser radiation, especially in

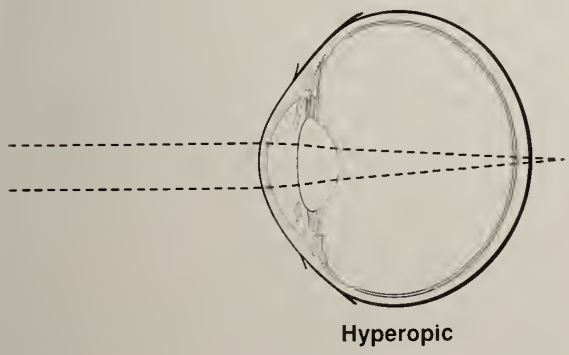


Figure 2.—The ray diagram of a hyperopic eye shows that the refracting power of the eye is too weak. The light rays from a distant object focus to a point behind the retina.

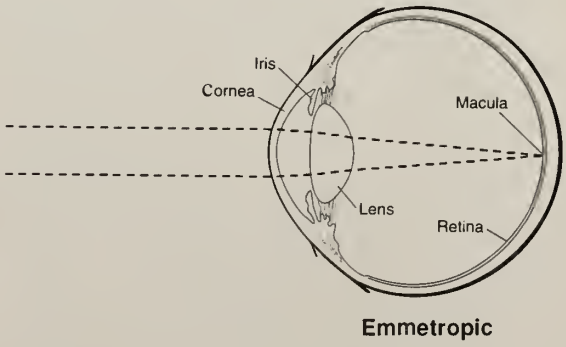


Figure 3.—The ray diagram of an emmetropic eye shows that the refracting power of the eye is perfect. The light rays from a distant object focus directly on the retina.

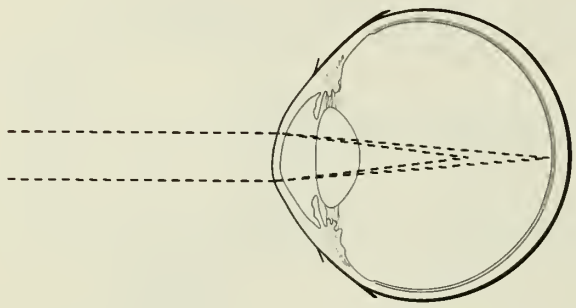


Figure 4.—The ray diagram of an astigmatic eye shows that in astigmatism, the anterior refracting surface of the eye is slightly elliptical rather than spherical. This causes light rays from a distant object to focus at 2 discrete points in the eye.

TABLE 1.—*Advantages and Disadvantages of Laser In Situ Keratomileusis Versus Photorefractive Keratectomy (PRK)*

Advantages
Rapid visual rehabilitation
Minimal pain or discomfort
Low incidence of haze
Intact Bowman's membrane and epithelium
More predictable with high levels of myopia
Disadvantages
More serious potential complications
More difficult to perform than PRK
Steep surgical learning curve
More costly
Possible maintenance problems with instrumentation

the ultraviolet light spectrum. Studies have been done showing that the 193-nm excimer laser is neither mutagenic nor carcinogenic.[9,10] This may be in part a result of shielding of the nucleus by the cell's cytoplasm.

Indications and Contraindications for PRK and LASIK

Currently, the use of PRK and LASIK to treat low to moderate myopia is approved in the United States. This includes for patients older than 18 years with refractive errors ranging from (1.0 to (12.0 diopters (D) of myopia. As much as 4 D of astigmatism can be corrected at the same time. Studies of PRK and LASIK for the treatment of moderate and high myopia are currently ongoing.

Preoperative patient evaluation is of utmost importance in determining eligibility for the PRK and LASIK procedures. Such an evaluation should include multiple refractions and a complete refractive history. Both subjective and cycloplegic refractions should be obtained, and the surgeon must be assured that the refraction is stable. This can be ascertained by reviewing the patient's medical record, inspecting old glasses, and checking refraction more than once.

A thorough medical and ocular history and a complete ocular examination are necessary to ensure the selection of suitable candidates for PRK and LASIK. Systemic conditions that are an absolute contraindication for PRK and LASIK include collagen vascular diseases such as rheumatoid arthritis, systemic lupus erythematosus, and polyarteritis nodosa because of the risk of inflammatory wound healing following PRK. Relative medical contraindications to PRK and LASIK include immunodeficiency of any cause because of the risk of aberrant wound healing and a predisposition to infection and diabetes mellitus because of the tendency for the refraction to fluctuate with the blood glucose level and a possible difficulty in healing corneal epithelial defects. Pregnant or nursing women are excluded because of possible instability of their refractive error. Eye-specific absolute contraindications include ocular surface disorders with anticipated corneal healing problems such as the Stevens-Johnson syndrome, cicatricial ocular pemphigoid, and prior chemical corneal burns. Patients with keratoconus and other ectatic corneal dystrophies often present to a refractive surgeon because of poor vision with spectacles and contact lenses. These conditions are an absolute contraindication for refractive surgery and should be identified during preoperative screening with the aid of computerized corneal topographic analysis.[11–13] Patients with evolving cataracts should also be excluded if cataract extraction is anticipated because appropriate selection of the intraocular lens power at the time of cataract extraction would obviate the need for PRK and LASIK. A history of herpes simplex keratitis is a relative contraindication because of the risk of the reactivation of keratitis following PRK and LASIK.[14,15]

Further investigation will help to identify preoperative characteristics associated with the outcome of PRK and LASIK. Aging of the patient and higher attempted PRK corrections have been shown to be independent preoperative characteristics associated with less likelihood of 20/40 uncorrected visual acuity and overcorrection postoperatively.[16] Clearly more research in this area is warranted.

Having established a patient's suitability for PRK and LASIK, appropriate informed consent is required, as in any surgical procedure. Such informed consent should delineate both the possible optical (such as glare or halo) and physical (such as scarring) complications of the procedure. The patient should also have a realistic expectation of the refractive outcome and understand that no refractive procedure can absolutely guarantee "perfect" vision.

Mechanisms of Laser Delivery

The clinical excimer laser comprises the following components: gases, power source, laser cavity, beam-forming optics, delivery system, aiming system, and surgical microscope.

For most current excimer laser systems, the initial pulse delivered from the laser cavity is a broad rectangular beam

of irregular energy level. For clinical use, this beam needs to be homogenized to yield a consistent energy over the entire delivery area. In the absence of a smooth and consistent beam energy, ablation rates could vary over the treatment area. In addition, the beam needs to be masked in two dimensions to the appropriate size and shape. Such beam homogenization and shaping are accomplished through a number of beam-shaping optics in the optical train of the laser. In addition, a diaphragm[17] interposed within this optical train masks the beam, causing it to be delivered as a circular spot of chosen diameter.

Current excimer lasers in clinical use operate at energy levels of about 160 to 180 millijoules (mJ) and a pulse rate of 5 to 10 pulses per second. The expected ablation rate of corneal tissue averages approximately 0.25 (m per pulse for a laser operating at 180 mJ per cm^2.[18–20]

To achieve refractive correction, the excimer laser energy is applied to the patient's cornea in a controlled manner to sculpt the appropriate tissue lens from the corneal surface for refractive corrections. This is accomplished in most units by a diaphragm interposed in the optical rail of the system, which expands as the treatment proceeds. Consecutively less tissue is thus removed from the center to the periphery of the ablation zone, with consequent flattening of the corneal surface. The pace of diaphragm opening and the duration of the procedure are determined by variables programmed into the laser's computer control.

Other strategies have been and are currently being developed to sculpt the corneal surface for refractive computer control. An ablatable mask (Summit Technology, Waltham, MA) is a polymethylmethacrylate lens interposed between the laser and the patient.[21–24] This mask is progressively ablated by the incoming laser beam. A concave mask is thus completely ablated centrally before peripherally. As the mask shield to the incoming beam is progressively ablated away, the optical power of the mask is transferred to the corneal surface. A toric mask can also be used to treat myopic astigmatism. Other laser strategies include a small scanning beam (such as Laser Sight , Orlando, FL) or a scanning slit (such as Nidek, Gamagori, Japan) that can be programmed to properly ablate the desired tissue. Strategies for correcting astigmatism include the ablatable mask, expandable slits (correcting cylindrical errors), and elliptical diaphragms for toric ablations. In all such lasers, the goal is to remove a spherocylindrical tissue lens from the corneal surface.

Another important factor in the development of the clinical excimer laser system is the modality of laser-eye coupling. Some investigators initially used a variety of handheld fixation devices and suction rings to stabilize a patient's eye. The manual fixation techniques have been abandoned, and the procedure is performed using simple patient fixation, directing the patient to fixate on a target coaxial with the incoming laser beam. Self-fixation yields better centration of the procedure than does actual physical fixation of the eye.[25] More recently, laser-eye coupling has been achieved by a variety of eye-tracking devices that have been developed to allow the laser to follow the eye in real time, thus minimizing the effects of eye movements during the procedure.

PRK Procedure and Postoperative Management

Preoperatively, the operative eye is labeled, and the contralateral eye is patched. This is to ensure that the patient maintains fixation with the operative eye and does not inadvertently fixate with the fellow eye. The refractive correction is confirmed. Mild sedation may be given to the patient before the operation. The patient is positioned on the excimer laser chair. A topical anesthetic is applied in multiple applications, and then a lid speculum is placed. The surgeon should ensure that the patient is comfortable and able to cooperate during the treatment. The patient is then properly aligned under the microscope of the excimer laser. In general, the patient is asked to fixate on a light that is coaxial with the incoming laser beam. The patient should then be reassured about the snapping sound of the laser and the odor associated with the ablation of corneal tissue. A round optical zone marker is used to mark the border of epithelium to be debrided. The epithelium is then carefully removed using one of a variety of methods, including manual scraping, rotating brushes, or the excimer laser itself (transepithelial technique). With all techniques, care is taken not to damage Bowman's layer. Moreover, the basal epithelial cells must be meticulously removed because residual epithelium would block the incoming beam and lead to uneven ablation. On the removal of epithelium—generally about 7 mm in diameter to accommodate a 6.0- to 6.5-mm laser optical zone size—centration is assured and the foot pedal of the laser depressed. A typical treatment may take approximately 200 laser pulses, 20 seconds at 10 Hz or 40 seconds at 5 Hz.

At the end of the procedure, a combination antibiotic and steroid solution, a topical nonsteroidal drop, and a bandage contact lens are placed in the patient's eye. The use of topical nonsteroidal anti-inflammatory agents and soft contact lenses have been shown to decrease postoperative pain following PRK.[26] Patients may be given oral nonsteroidal agents or narcotics and sleeping medications to make their first night comfortable. The patient is observed closely until the epithelium is healed, generally by 72 hours. On epithelial healing, a tapering regimen of corticosteroids is generally used for the first several months. The necessity and appropriate use of steroids remains a matter of controversy. A randomized double-masked study of the use of topical corticosteroid after PRK failed to show a sustained benefit compared with placebo after the cessation of therapy.[27] Other authors, however, have reported a significant role for topical corticosteroids in modulating postoperative wound healing.[28] Further studies may clarify the specific role of topical corticosteroid use in the postoperative management of PRK.

Clinical Results

The excimer laser underwent extensive clinical studies in the United States for about six years before receiving

approval by the Food and Drug Administration in October 1995. The initial studies focused on the correction of myopia in the range of 1.0 to 7.75 D.[29–31] Other investigators have looked at the use of the excimer laser for the correction of higher myopia[32–38] and astigmatism.[21,23,39–41] For a refractive procedure such as PRK, there are four important indices of outcome: the likely postoperative uncorrected visual acuity and predictability, stability, and safety of the procedure.

A general review of the literature shows uncorrected visual acuity following PRK in patients with lower degrees of myopia to range from 80% to 95% of patients with uncorrected visual acuity of 20/40 or better and 50% to 70% of patients at 20/20 or better. Recent studies report better results than investigations in the earlier phases of clinical excimer development, suggesting improvement of the PRK procedure. In phase III clinical trials, for instance, the use of Summit and VISX, Inc. (Santa Clara, CA) resulted in uncorrected visual acuities of 20/40 in more than 95% of eyes.[29–31]

The predictability of PRK is an indication of the refractive accuracy and is usually reported as the percentage of eyes achieving a correction within (0.50 D (or (1.00 D) of the desired refractive correction. For low myopia, about half of patients fall within 0.5 D of attempted correction, about three quarters of patients within 1.0 D, and about 95% of patients within 2 D of attempted correction. Studies of higher degrees of myopia show somewhat less predictability and postoperative uncorrected vision.[32–38]

Stability data for PRK are important for two reasons. The interval between the surgical procedure and a stable refraction allows the determination of the earliest reasonable time when reoperation might be considered for residual refractive errors. The long-term stability data for refractive surgical procedures allow accurate refractive correction with minimal risk of future large changes in refraction. For example, ten-year postoperative radial keratotomy data have shown that a proportion of patients became hyperopic long after their original operation to reduce myopia.[42] Studies of PRK, to date, have not shown this progressive hyperopia effect. In the early wound healing phase, many patients who have had excimer laser therapy regress somewhat, appearing to plateau at a relatively stable correction after about six months. Such stabilization may take longer in patients with higher diopter corrections. Stability and ultimate outcome may be affected by a patient's wound healing pattern. Most patients follow the typical pattern of slight regression early in the course, with subsequent stabilization. Better understanding of the individual wound healing response may suggest pharmacologic interventions to modulate the outcome following PRK.

Safety is typically reported as the percentage of eyes losing two or more lines of best spectacle-corrected visual acuity on the Snellen chart as the result of surgical treatment. In a recent report of the outcome of PRK for low, moderate, and high myopia in 504 eyes,[36] for myopia below (5.00 D, 4% of eyes lost two or more lines of best-corrected visual acuity; for myopia of between (5.00 and (10.00 D, 8% of eyes lost two or more lines; and for PRK above (10.00 D, 22% of eyes lost two or more lines of best spectacle-corrected visual acuity. The increased loss of best-corrected visual acuity observed with PRK corrections of high myopia is usually attributed to scarring. Future refinements in PRK laser ablation may reduce the likelihood of this complication.

Excimer laser PRK has also been used following other refractive surgical procedures such as radial keratotomy. Eyes with residual refractive errors following refractive keratotomy have been treated with the excimer laser to achieve better correction. In a large, prospective, multicenter clinical trial to evaluate the safety and efficacy of PRK following previous refractive surgery (primarily refractive keratotomy),[43] there was a high incidence of postoperative corneal scarring and loss of best spectacle-corrected visual acuity. Consequently, PRK should probably not be performed in eyes previously treated with refractive keratotomy.

Complications

Complications of refractive surgical procedures such as PRK and LASIK can be considered primarily optical or "physical." Optical complications include glare, halo, decreased contrast sensitivity, and diplopia. Glare and halo symptoms are likely due to the optical effects of light passing through the border between centrally treated and peripherally untreated cornea. An eye with a larger pupil would be more likely to manifest the symptoms of glare and halo, especially at night when the pupillary diameter is greatest.

Physical complications of PRK and LASIK include scarring, microbial keratitis, and sterile keratitis (infiltrates). Some degree of corneal wound healing after PRK is indicative of anticipated corneal wound healing. More substantial haze and scarring indicate aggressive wound healing and may lead to the regression of effect and loss of best spectacle-corrected visual acuity, as well as optical effects such as decreased contrast sensitivity, diplopia, glare, and halo. Corneal haze typically decreases during the first 12 months following PRK. Microbial keratitis is an unlikely complication of refractive surgical procedures in general and has been reported to occur in 1 of 2,400 cases of refractive keratotomy.[44] It requires immediate culture of corneal scrapings and intensive topical therapy with fortified broad-spectrum antibiotics. Scarring following the resolution of infection may limit best spectacle-corrected visual acuity and might in theory require corneal transplantation. Since the use of soft contact lenses and topical nonsteroidal anti-inflammatory medications to ameliorate pain during the initial 72 hours after PRK, the occurrence of sterile infiltrates has been reported,[26,45,46] which poses a diagnostic dilemma to ophthalmologists. Therapy for such sterile infiltrates includes the use of topical corticosteroids, which might exacerbate a case of unrecognized microbial keratitis. It is imperative, therefore, that microbial keratitis be ruled

out before the use of topical corticosteroids is contemplated for postoperative subepithelial infiltrates.

Correction of Astigmatism

Multiple studies have demonstrated the safety and efficacy of using the excimer laser to correct myopic astigmatism.[47–55] This procedure is labeled toric PRK or photoastigmatic refractive keratectomy and involves preferential reshaping of the cornea along a specified axis by either a nonspherical (elliptical) ablation or an ablatable mask. With current nomograms, 44% to 94% of cases of astigmatism can be corrected,[47–49,51–53] and 55% to 93% of eyes have an uncorrected visual acuity of 20/40 or better.[47,48,51–56]

In a Food and Drug Administration phase III clinical trial evaluating the safety and efficacy of photoastigmatic keratectomy using the Summit Apex Plus excimer laser in 93 eyes, a 90% reduction in compound myopia (spherical equivalent) and a 64% reduction in myopic astigmatism were seen at one-year follow-up.[56] In these patients, 81% of eyes were within 1.0 D of attempted correction, and 93% had an uncorrected visual acuity of 20/40 or better. Five percent lost more than two lines of best spectacle-corrected visual acuity. All eyes with haze had 20/20 or better best-corrected visual acuity. Contrast sensitivity function was temporarily diminished but returned to preoperative levels by 6 to 12 months.[57]

Excimer Laser In Situ Keratomileusis

During recent years, LASIK has become the procedure of choice for moderate to high levels of myopia among refractive surgeons. This procedure combines the developments made in lamellar surgery during the past 50 years with the technology and accuracy of the excimer laser. It involves the use of a microkeratome to create a superficial corneal flap, subsequent stromal ablation of the exposed corneal bed with the excimer laser, and repositioning of the corneal flap.

Historically, the foundation for LASIK is largely credited to Jose Ignacio Barraquer, MD. In the late 1940s, Barraquer performed freehand lamellar dissection in conjunction with the excision of stroma . Since then, many refinements have been made in lamellar surgery, including the use of the automated microkeratome and the development of the excimer laser. In 1988, Pallikaris initiated the use of the excimer laser in studies on rabbit eyes.[58] This led to his investigation of the laser in sighted human eyes in 1991. Many recent studies have demonstrated the effectiveness of LASIK in reducing myopia.[59–75] Currently, LASIK is performed on hundreds of thousands of people with myopia worldwide.

Patient Selection

Typically, LASIK had been used for moderate to high levels of myopia (4.0 to 16.0 D) in which PRK may yield suboptimal results. With improvements in surgical techniques and stable visual outcomes reported following LASIK, however, it is now being successfully used by many refractive surgeons to treat the low-level range of myopia as well.[61,62] As with PRK, patients must be older than 18 years, demonstrate stability in cycloplegic refraction for at least 12 months, and have a central corneal thickness not less than 500 (m for myopia less than 10 D and not less than 550 (m for myopia of 10 to 16 D. Patients with as much as 7.0 D of hyperopia and 7.0 D of astigmatism may also be candidates.[65]

Absolute contraindications include eyes with corneal disorder in shape, thickness, or inflammatory status. Thus, eyes with keratoconus; corneal ectasias; and corneas that are thin, active, or that have been recently inflamed (that is, with herpetic keratitis) should be excluded. Relative contraindications include patients with systemic vasculitis, autoimmune disease, collagen disorders, and diabetes mellitus or other states with abnormal healing. In addition, in monocular patients, patients with unstable precorneal tear film such as in the sicca syndrome, and those with endothelial counts of less than 1,500 cells, the procedure should also be considered as relatively contraindicated.

Technique

After patient education and informed consent, a topical antibiotic drop and a topical anesthetic (proparacaine hydrochloride, 0.5% solution) are placed in the eye. After the patient is prepared and draped, a wire-lid speculum is placed in the operated eye. A LASIK marker is used to facilitate appropriate realignment of the flap. A LASIK pneumatic suction ring is placed on the eye, and the intraocular pressure is raised to greater than 65 mm of mercury. The microkeratome is positioned on its tracks and used to resect a 130- to 180-(m corneal flap with a 300-degree circumference. Depending on the type of microkeratome, the corneal flap may be hinged along the nasal or superior border of the cornea.

Using a spatula or a forcep, the flap is elevated along its hinged border, and the excimer laser is used to photoablate the stromal bed. The stromal bed is irrigated with an isotonic sodium chloride solution, and the flap is reapproximated using the corresponding epithelial markings of the flap and the limbus created by the LASIK marker. Drying the cut edges and allowing the cornea to set for approximately 2 to 5 minutes allows the flap to adhere to the underlying stromal bed without the need for sutures. The lid speculum and drapes are removed, and the adherence of the flap is assessed by asking the patient to blink.

Postoperatively, patients may wear a transparent eye shield and are asked to refrain from rubbing their eyes. They are given a short course of topical broad-spectrum antibiotics, topical steroids, and artificial tears. Patients are observed on the first postoperative day and regularly thereafter at the discretion of the refraction surgeon.

Clinical Results

Early Summit phase I investigations on excimer laser myopic keratomileusis yielded promising results. In six-month results on 47 eyes, 16 (34%) had an uncorrected

visual acuity of 20/25 or better, and 31 (66%) had 20/40 or better.[75] Since then, several recent studies have demonstrated the safety, stability, predictability, and efficacy of LASIK in reducing myopia.[59–75] With current technology and nomograms, uncorrected visual acuity on the first day following the surgical procedure is 20/40 or better in 86% of patients with low myopia and astigmatism.[60] With longer follow-up, a review of current literature demonstrates an uncorrected visual acuity of 20/20 or better in 30% to 80%[60,62,63,71,74] of eyes and 20/40 or better in about 70% to 90% of eyes.[60,62,74] The results vary depending on the level of preoperative myopia.[65]

Because LASIK is typically used to correct higher levels of myopia, consideration of the preoperative level of myopia and attempted correction should be noted before comparing results of PRK with those of LASIK in the current literature. In a recent study comparing PRK with LASIK in the treatment of low to moderate amounts of myopia ((1.25 to –6.00 D), at one-year follow-up, 83% (85/103 eyes) of eyes undergoing LASIK had an uncorrected visual acuity of 20/20 compared with 72% (221/307 eyes) of eyes treated with PRK.[63]

Predictability is also an important indicator of refractive surgical outcome. With the use of LASIK, 81% to 89% of eyes are within (1.0 D of attempted correction.[59,60,63] Predictability, however, decreases with increasing level of myopia.[62] In higher levels of myopia, 60% to 78% of eyes are within (1.0 D of attempted correction.[59,62,66,68,77]

As with PRK, there may be a subtle loss in contrast sensitivity following LASIK. This is measurable only with rigorous testing. These subtle losses, however, may return to preoperative states 3 months after LASIK and 6 to 12 months after PRK.[62] In addition, there may be some regression (about 0.5 D) within three months after LASIK. Higher levels of myopia may lead to a further regression.[66]

The LASIK procedure offers several advantages over PRK (Table 1). Unlike the extended postoperative recovery period after PRK, there is rapid visual rehabilitation after LASIK. On the first postoperative day following LASIK, 61% to 80% of patients will have uncorrected visual acuity of 20/40 or better, depending on the level of myopia.[58] In addition, patients usually have only mild irritative symptoms or foreign body sensation immediately following LASIK. Unlike with PRK, the incidence of corneal scarring and haze are substantially reduced after LASIK.[71,72]

Complications may occur following LASIK, however. The most common complication is undercorrection. As in any refractive surgical procedure, all patients should be educated about the procedure and have a realistic perception of the surgical outcome. In most cases, retreatment of undercorrection is straightforward and yields good results.[67] The most serious complications can occur during the creation of the corneal flap. Perforation into the anterior chamber with the microkeratome, with resultant intraocular damage to the lens, ciliary body, and iris has been reported. Mechanical complications may also arise: loss of suction, microkeratome malfunction, and poor surgical technique. This can result in a number of flap complications, including an irregular flap, complete excision of the flap with a resultant free flap, too thin a flap, too thick a flap, a buttonholed flap, and wrinkles in the flap. Raising the intraocular pressure during the intraoperative phase may also result in retinal hemorrhages and vein occlusions.

The loss of best spectacle-corrected visual acuity of more than one line of Snellen visual acuity may occur in 0% to 8.8 % of eyes undergoing LASIK.[59,68,72,74,75] This may result from irregular astigmatism, progressive myopic maculopathy, epithelial ingrowth, or other complications.

The limitations of surface refractive techniques such as PRK have led to the evolution of more complicated lamellar surgical procedures such as LASIK. This procedure is technically demanding and has a steep surgical learning curve. In expert hands, however, LASIK may be more effective than PRK in the treatment of moderate to high-level myopia with shorter postoperative visual rehabilitation, earlier stable and predictable outcomes, and less corneal haze.[63,75] Refinements in the microkeratomes, technology, software, and techniques will lead to further improvements in the precision of LASIK for the treatment of refractive error.

Conclusions

Modern excimer laser refractive surgery is an exciting field of medicine that provides ophthalmologists with a tool to lessen or eliminate patients' dependence on glasses and contact lenses. The field is a dynamic one with the introduction of newer, more advanced technology and surgical techniques at a rapid pace. These advances should enable refractive surgeons to treat patients with higher levels of nearsightedness, astigmatism, and hyperopia in the near future. As the technology and techniques improve, we should develop a better understanding of the importance of laser-tissue interactions, corneal wound healing, and the role of pharmacologic agents in modulating refractive outcomes. These advances should allow PRK and LASIK to become more predictable with fewer complications.

REFERENCES

1. Refractive Errors. Preferred Practice Patterns. American Academy of Ophthalmology, San Francisco, California; 1997

2. Trokel SL, Srinivasan R, Braren B. Excimer laser surgery of the cornea. Am J Ophthalmol 1983; 96:710–715

3. Burlamacchi P. Laser sources. In: Hillenkamp F, Pratesi R, Sacchi CA, eds. Lasers in biology and medicine. New York (NY): Plenum Press; 1980:1–16

4. Puliafito CA, Steinert RF, Deutsch TF, Hillenkamp F, Dehm EJ, Adler CM. Excimer laser ablation of the cornea and lens: experimental studies. Ophthalmology 1985; 92:741–748

5. Jellinek HH, Srinivasan R. Theory of etching of polymers by far-ultraviolet, high-intensity pulsed laser and long-term irradiation. J Phys Chem 1984; 88:3048

6. Kahle G, Stadter H, Seiler T, Wollensak J. Gas chromatograph/mass spectrometer analysis of excimer and erbium-YAG laser ablated human corneas. Invest Ophthalmol Vis Sci 1992; 33:2180–2184

7. Tuft SJ, Zabel RW, Marshall J. Corneal repair following keratectomy: a comparison between conventional surgery and laser photoablation. Invest Ophthalmol Vis Sci 1989; 30:1769–1777

8. Malley DS, Steinert RF, Puliafito CA, Dobi ET. Immunofluorescence study of corneal wound healing after excimer laser anterior keratectomy in the monkey eye. Arch Ophthalmol 1990; 108:1316–1322

9. Nuss RC, Puliafito CA, Dehm EJ. Unscheduled DNA synthesis following

excimer laser ablation of the cornea in vivo. Invest Ophthalmol Vis Sci 1987; 28:287–294

10. Kochevar IE. Cytotoxicity and mutagenicity of excimer laser radiation. Lasers Surg Med 1989; 9:440–445

11. Wilson SE, Klyce SD. Screening for corneal topographic abnormalities before refractive surgery. Ophthalmology 1994; 101:147–152

12. Wilson SE. Corneal topography of keratoconus. Cornea 1991; 10:2–8

13. Rabinowitz YS, McDonnell PJ. Computer-assisted corneal topography in keratoconus. J Refract Corneal Surg 1989; 5:400–408

14. Pepose JS, Laycock KA, Miller JK, Chansue E, Lenze EJ, Gans LA, et al. Reactivation of latent herpes simplex virus by excimer laser photokeratectomy. Am J Ophthalmol 1992; 114:45–50

15. Vrabec MP, Anderson JA, Rock ME, Binder PS, Steinert RF, Durrie DS, et al. Electron microscopic findings in a cornea with recurrence of herpes simplex keratitis after excimer laser phototherapeutic keratectomy. CLAO J 1994; 20:41–44

16. Hersh PS, Schein OD, Steinert R. Characteristics influencing outcomes of excimer laser photorefractive keratectomy—Summit Photoreactive Keratectomy Phase III Study Group. Ophthalmology 1996; 103:1962–1969

17. McDonald MB, Frantz JM, Klyce SD, Salmeron B, Beuerman RW, Munnerlyn CR, et al. One-year refractive results of central photorefractive keratectomy for myopia in the nonhuman primate cornea. Arch Ophthalmol 1990; 108:40–47

18. Krueger RR, Trokel SL. Quantitation of corneal ablation by ultraviolet laser light. Arch Ophthalmol 1985; 103:1741–1742

19. Krueger RR, Trokel SL, Schubert HD. Interaction of ultraviolet laser light with the cornea. Invest Ophthalmol Vis Sci 1985; 26:1455–1464

20. Seiler T, Kriegerowski M, Schnoy N, Bende T. Ablation rate of human corneal epithelium and Bowman's layer with the excimer laser (193 nm). J Refract Corneal Surg 1990; 6:99–102

21. Hersh PS, Patel R. Correction of myopia and astigmatism using an ablatable mask. J Refract Corneal Surg 1994; 10 Suppl:250–254

22. Maloney R, Friedman M, Harmon R, Hagen K. A prototype ablatable mask delivery system for the excimer laser. Ophthalmology 1993; 100:542–549

23. Cherry PM, Tutton MK, Bell A, Neave C, Fichte C. Treatment of myopic astigmatism with photorefractive keratectomy using an erodible mask. J Refract Corneal Surg 1994; 10 Suppl:239–245

24. Friedman MD, Bittenson S, Brodsky L, et al. OmniMed II: a new system for use with the emphasis erodible mask. J Refract Corneal Surg 1994; 10 Suppl:267–273

25. Terrell J, Bechara SJ, Nesburn A, Waring GO, Macy J, Maloney RK. The effect of globe fixation on ablation zone centration in photorefractive keratectomy. Am J Ophthalmol 1995; 119:612–619

26. Sher NA, Frantz JM, Talley A, et al. Topical diclofenac in the treatment of ocular pain after excimer photorefractive keratectomy. J Refract Corneal Surg 1993; 9:425–436

27. Gartry DS, Kerr MM, Marshall J. The effect of topical corticosteroids on refraction and corneal haze following excimer laser treatment of myopia: an update—A prospective, randomized double-masked study. Eye 1993; 7(pt 4):584–590

28. Fagerholm P, Hamberg NH, Tengroth B, Epstein D. Effect of postoperative steroids on the refractive outcome of photorefractive keratectomy for myopia with the Summit excimer laser. J Cataract Refract Surg 1994; 20 Suppl:212–215

29. Maguen E, Salz JJ, Nesburn AB, Warren C, Macy JI, Papaioannou T, et al. Results of excimer laser photorefractive keratectomy for the correction of myopia. Ophthalmology 1994; 101:1548–1556

30. Talley AR, Hardten DR, Sher NA, Kim MS, Douighman DJ, Carpel E, et al. Results one year after using the 193-nm excimer laser for photorefractive keratectomy in mild to moderate myopia. Am J Ophthalmol 1994; 118:304–311

31. Dutt S, Steinert RF, Raizman MB, Puliafito CA. One-year results of excimer laser photorefractive keratectomy for low to moderate myopia. Arch Ophthalmol 1994; 112:1427–1436

32. Carson CA, Taylor HR. Excimer laser treatment of high and extreme myopia. Arch Ophthalmol 1995; 113:431–436

33. Cho YS, Kim CG, Kim WB, Kim CW. Multistep photorefractive keratectomy for high myopia. J Cataract Refract Surg 1993; 9 Suppl:37–41

34. Ditzern K, Anschutz T, Schroder E. Photorefractive keratectomy to treat low, medium, and high myopia: a multicenter study. J Cataract Refract Surg 1994; 20 Suppl:234–238

35. Kim HM, Jung HR. Multizone photorefractive keratectomy for myopia of 9 to 14 diopters. J Refract Surg 1995; 11(3 suppl):S293–S297

36. McCarty CA, Aldred GF, Taylor HR. Comparison of results of excimer laser correction of all degrees of myopia at 12 months postoperatively—The Melbourne Excimer Laser Group. Am J Ophthalmol 1996; 121:372–383

37. Rogers CM, Lawless MA, Cohen PR. Photorefractive keratectomy for myopia more than (10 diopters. J Refract Corneal Surg 1994; 10 Suppl:S171–S173

38. Sher NA, Hardten DR, Fundingsland B, DeMarchi J, Carpel E, Doughman DJ, et al. 193-nm excimer photorefractive keratectomy in high myopia. Ophthalmology 1994; 101:1575–1582

39. Taylor HR, Kelly P, Alpins N. Excimer laser correction of myopic astigmatism. J Cataract Refract Surg 1994; 20 Suppl:243–251

40. Spigelman AV, Albert WC, Cozean CH, Johnson DG, McDonnell PJ, Pender PM, et al. Treatment of myopic astigmatism with the 193 nm excimer laser utilizing aperture elements. J Cataract Refract Surg 1994; 20 Suppl:258–261

41. Pender PM. Photorefractive keratectomy for myopic astigmatism: phase IIA of the Federal [sic] Drug Administration study (12 to 18 months follow-up)—Excimer Laser Study Group. J Cataract Refract Surg 1994; 20 Suppl:262–264

42. Waring GO 3d, Lynn MJ, McDonnell PJ. Results of the prospective evaluation of radial keratotomy (PERK) study 10 years after surgery. Arch Ophthalmol 1994; 112:1298–1308

43. Maloney RK, Chan W, Steinert R, O'Connell M. A multicenter trial of photorefractive keratectomy for residual myopia after previous ocular surgery. Ophthalmology 1995; 102:1042–1053

44. Cottingham AJ, Berkeley RG, Nordan LT. Bacterial corneal ulcers following keratorefractive surgery: a retrospective study of 14,163 procedures. Presented at the Ocular Microbiology and Immunology Group Meeting, San Francisco, California, 1986

45. Teal P, Breslin C, Arshinoff S, Edmison D. Corneal subepithelial infiltrates following excimer laser photorefractive keratectomy. J Cataract Refract Surg 1995; 21:516–518

46. Probst LS, Machat JJ. Corneal subepithelial infiltrates following photorefractive keratectomy (Correspondence). J Cataract Refract Surg 1996; 22:281

47. Gallinaro C, Toulemont PJ, Cochener B, Colin J. Excimer laser photorefractive keratectomy to correct astigmatism. J Cataract Refract Surg 1996; 22:557–563

48. Carones F, Brancato R, Morico A, Venturi E, Gobbi PG. Compound myopic astigmatism correction using a mask in-the-rail excimer laser delivery system: preliminary results. Eur J Ophthalmol 1996; 6:221–233

49. Kremer I, Gabbay U, Blumenthal M. One-year follow-up results of photorefractive keratectomy for low, moderate, and high primary astigmatism. Ophthalmology 1996; 103:741–748

50. Kim YJ, Sohn J, Tchah H, Lee CO. Photoastigmatic refractive keratectomy in 168 eyes: six-month results. J Cataract Refract Surg 1994; 20:387–391

51. Goggin MJ, Kenna PF, Lavery FL. Photoastigmatic refractive keratectomy for compound myopic astigmatism with a Nidek laser. J Refract Surg 1997; 13:162–166

52. Hamberg-Nystrom H, Fagerholm PP, Tengroth BM, Viding AV. One year follow-up of photoastigmatic keratectomy (PARK) with the VISX 20/20 excimer laser. Ophthalmic Surg Laser 1996; 27(suppl):S499–S502

53. Tasindi E, Talu H, Ciftci F, Acar S. Excimer laser photorefractive keratectomy (PRK) in myopic astigmatism. Eur J Ophthalmol 1996; 6:121–124

54. Kaskaloglu M. Early results of photorefractive keratectomy for myopic astigmatism. J Refract Surg 1996; 12:S258–S260

55. Snibson GR, Carson CA, Aldred GF, Taylor HR. One-year evaluation of excimer laser photorefractive keratectomy for myopia and myopic astigmatism—Melbourne Excimer Laser Group. Arch Ophthalmol 1995; 113:994–1000

56. Haw WW, Manche EE. Toric PRK using the Summit Apex Plus excimer laser with an erodible mask—Phase III of an FDA clinical trial. Presented at the American Society of Cataract and Refractive Surgery meeting, San Diego, California, April 21, 1998

57. Haw WW, Manche EE. Visual performance following toric PRK using the Summit Apex Plus excimer laser. Presented at the American Society of Cataract and Refractive Surgery meeting, San Diego, California, April 19, 1998

58. Pallikaris IG, Papatzanki ME, Sigamous DS, et al. A corneal flap technique for laser in situ keratomileusis. Human Studies. Arch Ophthamol 1991; 145:1699-1702

59. Lindstrom RL, Hardten DR, Chu YR. Laser in situ keratomileusis (LASIK) for the multicenter phase I treatment of low, moderate, and high myopia. Trans Am Ophthalmol Soc 1997; 95:285–296

60. Zaldivar R, Davidorf JM, Shultz MC, Oscherow S. Laser in situ keratomileusis for low myopia and astigmatism with a scanning spot excimer laser. J Refract Surg 1997; 13:614–619

61. Danasoury MA, Waring GO, Maghraby A; Mehrez K. Excimer laser in situ keratomileusis to correct compound myopic astigmatism. J Refract Surg 1997; 13:511–520

62. Pesando PM, Ghiringhello MP, Tagliavacche P. Excimer laser in situ keratomileusis for myopia. J Refract Surg 1997; 13:521–527

63. Wang Z, Chen J, Yang B. Comparison of laser in situ keratomileusis and photorefractive keratectomy to correct myopia from –1.25 to –6.00 diopters. J Refract Surg 1997; 13:528–534

64. Pirzada WA, Kalaawry H. Laser in situ keratomileusis for myopia of (1 to (3.50 diopters. J Refract Surg 1997; 14(suppl):S425–S426

65. Buratto L, Ferrari M. Indications, techniques, results, limits and complications of laser in situ keratomileusis. Curr Opin Ophthalmol 1997; 8:59–66

66. Perez-Santonja JJ, Bellot J, Claramonte P, Ismail MM, Alio JL. Laser in situ keratomileusis to correct high myopia. J Cataract Refract Surg 1997; 23:372–385

67. Condon PI, Mulher M, Fulcher T, Foley-Nolan A, O'Keefe M. Laser intrastroma keratomileusis for high myopia and myopic astigmatism. Br J Ophthalmol 1997; 81:199–206

68. Marinho A, Pinto MC, Pinto R, Vaz F, Neves MC. Lasik for high myopia:

one-year experience. Ophthalmic Surg Lasers 1996; 27(suppl):S517–S520

69. Pallikaris IG, Siganos DS. Laser in situ keratomileusis to treat myopia: early experience. J Cataract Refract Surg 1997; 23:39–49

70. Kim HM, Jung HR. Laser assisted in situ keratomileusis for high myopia. Ophthalmic Surg Lasers 1996; 27(suppl):S508–S511

71. Helmy SA, Salah A, Badawy TT, Sidky AN. Photorefractive keratectomy and laser in situ keratomileusis for myopia between 6.0 and 10.00 diopters. J Refract Surg 1996; 12:417–421

72. Guell JL, Muller A. Laser in situ keratomileusis (LASIK) for myopia from (7 to (18 diopters. J Refract Surg 1996; 12:222–228

73. Fiander DC, Tayfour F. Excimer laser in situ keratomileusis in 124 myopic eyes. J Refract Surg 1995; 11(suppl):S234–S238

74. Salah T, Waring GO, el-Maghraby A, Moadel K, Grimm SB. Excimer laser in situ keratomileusis (LASIK) under a corneal flap for myopia of 2 to 20 D. Trans Am Ophthalmol Soc 1995; 93:163–190

75. Pallikaris IG, Siganos DS. Excimer laser in situ keratomileusis and photorefractive keratectomy for correction of high myopia. J Refract Corneal Surg 1994; 10:498–510

76. Brint SF, Ostrick DM, Fisher C, Slade SG, Maloney RK, Epstein R, et al. Six-month results of the multicenter phase I study of excimer laser myopic keratomileusis. J Cataract Refract Surg 1994; 20:610–615

77. Knorz MC, Liermann A, Seiberth V, Steiner H, Wiesinger B. Laser in situ keratomileusis to correct myopia of (6 to (29.00 diopters. J Refract Surg 1996; 12:575–584

Epitomes

Important Advances in Clinical Medicine

Psychiatry

Irwin I. Rosenfeld, MD, Section Editor

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in psychiatry. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, as to both scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in psychiatry that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Psychiatry of the California Medical Association, and the summaries were prepared under the direction of Dr Rosenfeld and the Panel.

Advances in Mood Stabilizing Medications

In the past decade, lithium's limitations as an acute and prophylactic treatment for patients with manic-depressive illness have been recognized. In addition, studies have revealed that about 50% of patients may show only a partial therapeutic response and inadequate prophylactic effect. Certain diagnostic subtypes (dysphoric mania, rapid cycling) have notably poor response rates to lithium therapy,and a substantial number of patients cannot tolerate its side effects or are unable to achieve blood levels that are necessary for complete suppression of symptomatology. This experience has necessitated the study of adjunctive and alternative treatment options to lithium.

Several anticonvulsants have emerged as major mood stabilizing alternatives to lithium therapy for bipolar illness. Data on carbamazepine and valproate indicate that while they appear to prevent manic and depressive episodes in patients inadequately responsive to lithium carbonate, they may not be sufficient for monotherapy. Two newer anticonvulsant agents, gabapentin and lamotrigine, have shown promise in the treatment of patients with bipolar disorders. Both gabapentin and lamotrigine differ from other mood regulators in two major ways: (1) their reported frequent effectiveness for treating resistant patients, and (2) their relatively benign side-effect profiles that make discontinuation due to side effects rare.

Gabapentin increases gamma amino butyric acid (GABA) turnover and whole blood serotonin, increases breakdown of glutamic acid, and modulates norepinephrine and dopamine in vivo. Case reports have described its potential psychiatric indications in bipolar disorder, panic disorder, generalized anxiety disorder and behavioral dyscontrol. The post-absorption half-life is 5–7 hours with rapid crossing of the blood brain barrier. The usual starting dose of gabapentin is 300 mg once a day; the dose is increased and rapidly titrated every three to five days to the mood stabilizing dose, which is most often between 900–2700 (up to 4800 reported) mg per day typically taken in divided doses. Therapeutic effect is noticed from within a week up to a month. Gabapentin is generally well tolerated. The most common side effects are sedation, dizziness, unsteadiness, nystagmus, ataxia, fatigue, tremor and diplopia, which stop when the drug is stopped.

Lamotrigine acts upon the voltage-dependent sodium channels, resulting in inhibited release of the excitatory neurotransmitters glutamate and aspartate, and stabilization of the neuronal membranes. Early reports suggest that lamotrigine may be beneficial in patients with treatment-resistant bipolar disorders, including mixed and rapid cycling illness. Its use in treating unipolar depression and anxiety disorders has not been extensively studied. The inhibition of glutamate may suggest a role for lamotrigine in mania following ischemic stroke. Usual initiating dose of lamotrigine is 25 mg once or twice a day, and this is increased by 25–50 mg every 1–2 weeks, to reach the usual effective dose range of 100–200 mg per day. Therapeutic effect is generally noticed within a month of starting treatment. The most commonly reported adverse effects of lamotrigine are dizziness, diplopia, ataxia, blurred vision, nausea, and vomiting. A severe morbilliform or maculopapular rash, developing within the first six weeks which is related to starting dose and escalation of titration, can be a special clinical hazard (rate in adults one in every thousand patients with higher incidence below age sixteen). These effects subside when medication is discontinued, but can be problematic to treat.

The principal advantage of gabapentin and lamotrigine over lithium is that routine serum monitoring of drug levels is not essential during therapy. However, as with all bipolar patients, one should be aware of a possible paradoxical switch to mania or provocation of rapid

cycling. Also, while gabapentin may be safely used in combination with depakote and carbamazepine, their doses need adjustment when lamotrigine is initiated. Valproic acid should be reduced in dosage before starting lamotrigine to decrease inhibition of metabolism and reduce the risk of rash. Due to enzyme induction, the dose of carbamzepine may need to be reduced when lamotrigine treatment is initiated. The relatively recent use of gabapentin and lamotrigine for mood disorders limits the information regarding their long term therapeutic efficacy, and potential emergent side effects.

Other modalities being studied as mood stabilizers include calcium channel blockers, and thyrotropin releasing hormone (TRH) plus other endogenous neuropeptides. Calcium channel blockers like verapamil and nimodipine are showing special promise for rapid and ultra rapid cycling. Preliminary findings have suggested that the dihydropyridine class of L-type calcium channel blockers, which includes nimodipine, isradipine etc., compared to the phenylalkalamine verapamil may have greater mood stabilizing effects, and potential as an alternative or adjunct to lithium. Preliminary data on TRH indicate possible acute anti-depressant, anti-anxiety, and anti-suicide effects.

Although the search for safer alternatives to lithium therapy in affective disorders is increasingly promising, further research of the newer mood stabilizing medications is warranted in order to establish their safety and efficacy.

BARTON J. BLINDER MD, PHD
SUVARNA BHAT, MD
VISANT A. SANATHARA
Irvine, California

REFERENCES

Dubovsky SL, Buzan RD. Novel alternatives and supplements to lithium and anticonvulsants for bipolar affective disorder. J Clin Psychiatry 1997; 58:224–242

Fatemi SH, et. al. Lamotrigine in rapid cycling bipolar disorder. J Clin Psychiatry 1997; 58:522–527

Sussman N. Gabapentin and lamotrigine: Alternative agents for the treatment of bipolar disorder. Prim Psychiatry 1997; 2:25–36

Traumatic Disorders—Contemporary Directions

EMOTIONAL REACTIONS to trauma have been recorded since ancient times. In this century, the study of World War I veterans ("shell shock"), World War II consequences ("traumatic neurosis"), and later DSM-I (Gross Stress Reaction), DSM-II ("Transient Situational Disturbance"), Holocaust Survivors ("Survivors' Syndrome"), and DSM-III (PTSD) all constituted additions to a crystallized modern understanding of trauma reactions.

Since 1980, when Post Traumatic Stress Disorder (PTSD) became part of the official psychiatric nomenclature (DSM-III), a concerted effort has been made by specialists in psychiatric trauma to legitimize PTSD as a complex psychiatric disorder. Trauma can result in a range of disorders. The most commonly associated conditions with trauma are: PTSD, Acute Stress Disorder, other Anxiety Disorders, Mood Disorders, Somatization Disorders, Dissociative Disorders, Substance Abuse, and Adjustment Disorders. On the other hand, early childhood exposure to severe trauma more often results in affective psychopathology with little resemblance to PTSD. The type of traumatic psychopathology may be determined by the interaction of factors: type of trauma, age of impact, preexisting biological vulnerability, and possibly the complexity of affected brain mechanisms.

Diagnosis of Post Traumatic Stress Disorder represents the prototype of traumatic disorders. The symptomatology includes a classical triad of symptoms: a) The re-experiencing of the traumatic event, b) Both persistent avoidance of stimuli associated with the trauma and numbing of general responsiveness, c) Symptoms of hyperarousal (difficulty falling asleep, insomnia, irritability, angry outbursts, etc.). These symptoms occur after the exposure via experiencing, witnessing, or confronting an event that is perceived as threatening and is accompanied by intense fear, horror, and helplessness. Prevalence of PTSD is 7.2 percent in the generation population. Between 50 and 90 percent of patients with PTSD have comorbid disorders such as anxiety, depression and alcohol abuse.

Other traumatic disorders include acute stress disorder, a condition that resembles PTSD but is characterized by a one-month duration (following the trauma) and includes significant dissociative symptoms. Anxiety disorders (more often panic disorders and generalized anxiety) are often the main psychiatric manifestation after traumatic stress. Most anxiety disorders occur more often in combination with other diagnoses rather than "pure culture" clinical forms. While, for example, major depression may not exhibit a different picture after a known traumatic stress, a history of traumatic stress may add additional biological abnormalities and may thus influence significantly the outcome of treatment.

After major traumatic events such as a catastrophe affecting an entire community, PTSD is relatively rare. Emotional manifestations of some kind are common, however. The majority of traumatized individuals will present a transient benign reaction characterized by terror, a sense of unreality, some depersonalization, some re-experiencing, transient anxiety, a sense of loss, and some preoccupation with images of the trauma that subsides within about 3 to 4 months. Risk factors for patients to PTSD after a community trauma include past psychiatric history, family psychiatric history, genetics, personality style such as neuroticism, introversion, personality disorder, history of trauma, low socioeconomic status, low intelligence, and even a family history of trauma.

PTSD, the prototype of traumatic disorders, is accompanied by biological markers such as an increase in blood pressure, pulse, glucocorticoid receptors, T3 and analgesia and reflect a marked sympathetic automatic overdrive, and a decrease in cortisol, alpha 2 adrenergic receptor activity, and stage three and four of sleep. In addition, acute stress is characterized by significant elevation of cortisol. Individuals suffering from chronic PSTD, on the other hand, have blunted plasma cortisol.

Recent and preliminary studies show that PTSD patients in veterans' hospitals have an average of 15 severe traumatic events in their lifetimes. Thus, in comparison to controls, individuals who develop PTSD are more likely to have had previous trauma. Finally, variants of PTSD occur. "Compassion fatigue," a form of traumatic disorder, may develop in health and mental health professionals who care for

patients with PTSD; "Disorder of extreme stress, not otherwise specified" (DESNOS or "Complex PTSD"), a condition that includes symptoms of PTSD associated with severe psychiatric complications, i.e., bipolar symptoms, psychosis, hallucinations, etc. also occurs. Secondary traumatization is another variant and refers to the occurrence of traumatic symptoms, more often PTSD, in individuals exposed to or who live with victims of traumatic stress.

In PTSD the process of memory consolidation may lead to continuous retraumatization, rendering PTSD a self-maintained condition similar to an autoimmune disorder. Early administration of beta blocking agents (limiting the adrenergic overdrive which is implicated in traumatic memory consolidation) and SSRIs (Fluoxetine, Sertraline, Paroxetine, Fluvoxamine), which work both on re-experiencing and avoidant sysmptoms, are now standard medical intervention. Long term use of minor tranquilizers is not indicated. Comorbid disorders have to be addressed at the same time (e.g., substance abuse). Most often clinicians are using a combination of dynamic and behavioral psychotherapy. Recalling the traumatic events in therapy or exposure to "reminders" has to be done carefully and gradually; therapists usually learn the amount of discomfort that such patients can tolerate. Other treatment modalities, e.g., EMDR (Eye Movement Desensitization Reprocessing) seem to have numerous enthusiasts but still remain to many authors controversial.

ANDREI NOVAC, MD
Newport Beach, California

REFERENCES

Goldenberg IM, White K, et al. The infrequency of "pure culture" diagnoses among the anxiety disorders. J. Clin. Psychiatry 1996; 57:528–533

Novac A, Hubert-Schneider S. Acquired vulnerability: Comorbidity in a patient population of adult offspring of holocaust survivors. Am J Forensic Psychiatry 1998; 19:45–58

When Chest Pain, Shortness of Breath, and Palpitations are Not Due to Cardiopulmonary Pathology

IT IS NOT UNCOMMON for the primary care physician, cardiologist, or emergency physician to see patients presenting with acute acute onset of chest pain, shortness of breath, palpitations, choking sensation, diaphoresis, trembling, paresthesias, lightheadedness, abdominal distress and fear of dying, only to find, after extensive and expensive workup, that there is no cardiopulmonary pathology present. Such patients often receive the diagnosis, "rule-out myocardial infarction," or "chest pain of unknown etiology." Panic disorder is characterized by recurrent and unexpected panic attacks (composed of at least four of thirteen symptoms, ten of which are listed above, and also include chills.

Panic disorder is defined by recurrent and unexpected panic attacks (composed of at least four of 13 symptoms, including chills or hot flashes, fear of losing control or going crazy, and de-realization or de-personalization) with at least one month of excessive concern about having another panic attack, or behavioral changes resulting from the attacks that are not substance-induced (e.g. precipitated by stimulants) and are not due to medical conditions (such as cardiac or vestibular disorders, hyperthyroidism, hyperparathyroidism, pheochromocytoma, or seizures.) Limited symptom attacks have fewer than four symptoms and are usually shorter and less severe. Panic attacks usually happen quickly (escalate in less than one minute and peak in less than 10 minutes) and typically last for 30 to 60 minutes, although some last for several hours. Nearly half of patients with panic disorder also have agoraphobia (fear of being in public places).

Panic disorder is common, with one-year prevalence at 1.5% of the population and lifetime prevalence at 2.5%. Women account for more than two-thirds of patients. Peak onset is from the late teens to mid-thirties, although it may come on at any age. There is a four to seven times greater incidence in first degree relatives.

The course of panic disorder is usually chronic, with waxing and waning, although one-third of patients go into complete remission. Co-morbid depression is common; two-thirds of panic disorder patients have concurrent major depressive disorder at some point in their illness, and one-third at any point in time. Depressed patients with panic disorder have a much higher suicide rate than those without panic disorder. Alcohol abuse occurs in one-third of panic disorder patients.

Various studies have pointed to α_2-adrenergic receptor dysfunction, postsynaptic serotonin receptor supersensitivity, blunted growth hormone response to Clonidine, and asymmetric blood flow and metabolism in the hippocampus (left lower than right) noted on PET scan. One study showed an elevation of neuropeptide Y in panic patients: neuropeptide Y is closely associated with noradrenergic activity in the central and peripheral nervous systems.

Hypochondriasis is common in panic patients. An average patient with panic disorder has 27 different unexplained symptoms. In various studies, 15% of patients in a vestibular disorder clinic and 20% of patients with dizziness had panic disorder, and panic patients were found to have a high incidence of gastrointestinal disturbance. Among patients referred for pulmonary function testing to a major medical center, 41% were found to have panic attacks, 11% were diagnosed with panic disorder, and 67% of patients with chronic obstructive pulmonary disease were found to have concurrent panic disorder. Of those patients seeing cardiologists for chest pain, 30–60% with negative workups have panic disorder; of those seeing gastroenterologists for irritable bowel syndrome 33–45% have panic disorder. While only 0.2% of those undergoing workup of pheochromocytoma actually have this condition, 67% have panic disorder.

Treatment of panic disorder has focused on antidepressants, benzodiazepines, and psychotherapy. Imipramine was found in several studies to have an excellent track record in the treatment of panic disorder with significant effects at moderate (1.5 mg/kg/D) to high (3 mg/kg/D) doses, with drop-out rates due to side effects 15% and 35% for moderate and high doses, respectively. Clomipramine at similar doses has also been shown to be very effective; other tricyclics and trazodone appear to be less effective. Monoamine oxidase inhibitors (MAOI), especially phenelzine, have shown similar efficacy. Due to the high side effect profile of tricyclics and MAOI's, and their high rate of fatality when taken in overdose, studies in the past few

years have examined newer antidepressants. Of the selective serotonin re-uptake inhibitors (SSRI) greater success has been noted with fluvoxamine and paroxetine than with sertraline, and least with fluoxetine, which was nevertheless better than placebo. Nefazodone has also been shown to be effective for panic disorder, especially at standard (460 mg/D) versus low (243 mg/D) doses, and better than imipramine (202 mg/D). Bupropion has been shown to be ineffective. Studies on venlafaxine and mirtazapine are underway.

All benzodiazepines have shown efficacy in the treatment of panic disorder, but many patients will show significant side effects with doses needed to control the disorder. Benzodiazepines are not recommended at the onset of an attack, since the action of the medication, which averages 30–60 minutes, is similar to that of the duration of the panic attack itself. However, in the few panic patients whose panic attacks last for several hours, an "as needed" approach may be the exception to this proscription. Average doses of alprazolam in panic disorder patients are 2 to 8 mg/D, with other benzodiazepines at commensurate levels. Studies show that gradual taper of benzodiazepines after several months of treatment resulted in almost universal withdrawal symptoms. A significant number of patients were unable to discontinue treatment. This is in contrast to antidepressants. In one study, only 18% of patients were able to discontinue alprazolam, whereas 82% were able to stop imipramine.

Cognitive behavioral treatment has been shown to be very helpful for panic disorder, especially with intermediate term treatment (18 sessions over six months) versus shorter term treatment, and especially in the hands of a skilled cognitive therapist. Exposure therapy has been shown to be helpful for concomitant agoraphobia, as well as other phobias, if present. At least two studies, however, have shown fluvoxamine superior to cognitive therapy in the treatment of panic disorder. Current practice would be to start with low dose SSRI and gradually titrate up to an effective dose. Severely anxious patients may be given benzodiazepines concurrently until antidepressant efficacy has been achieved, then tapered. Netazadone, imipramine or clomipramine, and pheuelzine, in thatorder would be reasonable alternatives if two or three SSRRs are either ineffective of not tolerated. The newer antidepressants (SSRRs and nefazadone) are better tolerated than the older ones (tricyclics and MAOIs), and are much safer. Cognitive behavioral therapy conducted simultaneously with pharmacotherapy will usually improve efficacy.

Successful treatment of panic disorder can lead to a 90% decrease in medical treatment costs and improved quality of patients' personal and professional lives.

IRWIN I. ROSENFELD, MD
Laguna Hills, California

REFERENCES

Ballenger J. Update in the treatment of panic. Am Soc Clin Pharm Prog Notes 1997; 8:34–40

Coplan JD, et. al. Clinical improvement with fluoxetine therapy and noradrenergic function in patients with panic disorder. Arch Gen Psychiatry 1997; 54:643–8

Zajecka JM. The effect of nefazodone on co-morbid anxiety symptoms associated with depression: experience and family practice in psychiatric out-patient settings. J Clin Psychiatry 1996; 57:10–14

Treatment Update in Geriatric Psychiatry

MAJOR DEPRESSION in older persons is distinguished by early- and late-onset. Early-onset depressions first occur earlier in life and tend to recur into late life. Late-onset major depression occurs for the first time after about age 60. In older persons, late-onset depression tends to be more chronic, to have either a short-lived or a partial treatment response to antidepressant medication, and to be more related to suicide than recurrence of early-onset depression. Two new findings add dimension to these observations: 1) a substantial proportion of late-onset depressions tend to foreshadow the development of a dementia such as Alzheimer's disease or vascular dementia; 2) the evolution of the concept of vascular depression. Despite the type of depression, it still develops within the context of life stress and lack of social support. The 1997 update on the 1991 NIH Consensus Development Conference on the Diagnosis and Treatment of Depression in Late Life further described the high degree of medical comorbidity and disability as well as the impact of depression on health services and resource use.

With the advent of structural MRI, subtle vascular changes in the brains of depressed older persons can be evaluated. Patients with late-onset depression tend to have hyperintense signals on T2 weighted MRI images in subcortical white matter, basal ganglia, and caudate and putamen nuclei. Small lesions (5 mm) in the left frontal lobes seem more closely associated with depression while larger left subcortical lesions of stroke patients seem related to post-stroke depression.

Although the concept of vascular depression requires further clarification, its relationship to ischemic vascular changes in the brain, and with vascular disease risk factors such as diabetes, hypertension, high cholesterol or lipid levels, as well as coronary artery disease and hypothyroidism seems rather consistent. Clinically defined vascular depression patients tend to have greater cognitive impairments (in verbal fluency and naming), functional disabilities, and psychomotor retardation, and less agitation, guilt feelings and insight than patients with non-vascular related depression.

With respect to depression in older persons , it has been recently recognized that older patients may not quite fulfill clinical criteria for major depression, having instead "minor" or "subsyndromal" depressions, but with clinical courses and responses to medication similar to that of major depression. These patients are as responsive to treatment with a serotonin-selective reuptake inhibitor such as fluoxetine as are patients with major depression, and also tend to relapse at a similar 50% rate when medication is discontinued.

The recent availability of atypical or unconventional neuroleptic medications such as risperidone (Risperidal), olanzepine (Zyprexa), and quetiapine (Seroquel) promises to increase the safety and effectiveness of treating older patients with either late-onset delusional disorders, or with behavioral complications of Alzheimer's disease and other dementias. Over 70% of patients with Alzheimer's disease develop behavioral problems such as delusions, agitation, and aggression that require psychotherapeutic medication. In the past, typical or conventional neuroleptics such as haloperidol or chloropromazine have been used but have important side effects, especially extrapyramidal motor signs and symptoms and tardive dyskinesia. The atypical neuroleptics are characterized by serotoninergic antagonism. Although they are different from each other the atypical neuroleptics are better tolerated than are conventional neoroleptics.

By the end of 1998, physicians should have a choice of four different cholinesterase inhibitors for the treatment of Alzheimer's disease. A substantial proportion of patients with Alzheimer's disease have improved cognition and improved activities of daily living with these medications. Unfortunately, although the drugs appear to improve symptoms, they do not seem to alter the course of the illness. There is new but uncontrolled evidence that cholinesterase inhibitors might also mitigate the emergence of some behavioral symptoms of the illness, including delusions, and may also be useful for patients with severe cognitive impairment.

Last year, the results of a randomized controlled trial indicated the potential efficacy of vitamin E and/or selegiline (Eldepryl) in altering the symptomatic course of Alzheimer's disease. Patients on either of the medications alone or in combination remained in the community and avoided nursing home placement about five to seven months longer than those on placebo. Although there was less deterioration of activities of daily living, there was no change in cognitive function, suggesting that it might be possible to change some elements of the illness without affecting the core cognitive clinical features.

Suggestions have been made that estrogen replacement therapy or anti-inflammatory therapy may delay the onset of Alzheimer's disease, because estrogen is neurotrophic to cholinergic neurons and inflammatory processes attend the progressive neurodegeneration. Although observational studies have supported this, there have yet to be adequate randomized clinical trials. Therefore, these approaches remain reasonable but unproven.

LON S. SCHNEIBER, MD
Los Angeles, California

REFERENCES

Alexopoulos GS, Meyers BS, Young RC, Kakuma T, Silbersweig D, Charlson M. Clinically defined vascular depression. Am J Psychiatry 1997; 154:562–565

Devanand DP, Kim MK, Nobler MS. Fluoxetine discontinuation in elderly dysthymic patients. Am J Geriatr Psychiatry 1997; 5:83–87

Krishnan KR, Hays JC, Blazer DG. MRI-defined vascular depression. Am J Psychiatry 1997; 154:497–501

Sano M, Ernesto C, Klauber MR, Schafer K, Woodbury P, Thomas R, Grundman M, Growdon J, Cotman CW, Pfeiffer E, Schneider L, Thal L. A controlled trial of selegiline, α-tocopherol or both as treatment for Alzheimer's Disease. N Engl J Med 1997; 336:1216–1222

Schneider LS, Farlow MR, Henderson VW, Pogoda JM. Effects of estrogen replacement therapy on response to tacrine in patients with Alzheimer's disease. Neurology 1996; 46:1580–1584

The New Antipsychotic Compounds: Is a Clinical Choice Algorithm Possible?

MOST DRUG TRIALS for schizophrenics have used conventional antipsychotics in the control treatment-arm of the experiment and have tended to involve narrowly defined, homogeneous schizophrenia subject populations. The newer antipsychotic medications (including clozapine) all have lower extrapyramidal toxicity than their conventional counterparts. The clinical groups, therefore, that have sensitivity to neurotoxic side effects (i.e. first break subjects, children, older patients, nonschizophrenic psychotic conditions) should derive the greatest benefit from this characteristic, but few studies address these groups. It is therefore not possible to make direct comparisons of effectiveness or toxicity among the various newer medications, particularly for the more "normal" clinical population, but some conclusions can be drawn, and a few predictions made.

Among the available novel agents, clozapine and quetiapine possess the lowest extrapyramidal toxicity, followed closely by olanzapine and then risperidone. When extrapyramidal toxicity dominates the clinical picture, clozapine or quetiapine should be the first choice. Other toxicities associated with clozapine, (blood dyscrasias, seizures, sedation, cardiotoxicity, etc.), however, prevent its easy clinical use, even in cases of severe acute extrapyramidal toxicity.

The newer agents also differ from conventional compounds along endocrinologic lines. Clozapine and quetiapine do not elevate prolactin, and olanzapine generally induces only a mild, and usually transient, prolactin elevation. Risperidone, on the other hand, elevates prolactin at least as much or more than its conventional counterparts. In clinical circumstances where prolactin elevation is of clinical concern, as in young or adolescent females, or patients with clinical intolerance of hyper prolactinemia—amenorrhea, galactorrhea, gynecomastia, testicular atrophy, erectile incompetence—clozapine, quetiapine, or olanzapine should be used. Again however, because of the predominance of other toxicities with clozapine, olanzapine and quetiapine would be superior first choices. Other toxicities that are of clinical significance and do vary among this class include sedation, weight gain, and cardiovascular toxicity. Sedation is most severe with clozapine, and is generally the titration-limiting characteristic of this compound. Olanzapine has somewhat more sedative potential than either risperidone or quetiapine but substantially less than clozapine.

Weight gain should be anticipated with most of the new compounds. Forty percent of patients treated with atypical drugs will experience a greater than 10% weight gain. Measures to avoid weight gain are consistently

more effective than those employed to induce weight loss. Clozapine and olanzapine seem to stimulate more weight gain than risperidone and quetiapine. All of these compounds increase weight more than the high potency conventional medications.

Cardiovascular toxicity has become a clinical concern because sertindole has been noted to produce more QT prolongation than conventional medications. Although a precise rank ordering of the risk of inducing ventricular arrhythmias is not known at this time, clozapine seems to have somewhat more potential than any of the other three compounds. Orthostatic hypotension with reflex tachycardia is the other major cardiovascular toxicity induced by these drugs. Here again, clozapine is the most difficult agent, followed distantly by the other three compounds.

Quetiapine's toxic profile, while favorable in most respects, contains a theoretical increased risk of eye complications, since its use in certain animal models results in the development of cataracts. This animal toxicity prompted the manufacturer and the FDA to advise slip lamp examinations before, and during, quetiapine treatment. Because the time course to the development of clinically significant cataracts is very slow, it is not our clinical habit to obtain a slip lamp examination before treatment. Instead, we perform routine clinical ophthalmoscopy before treatment (as we do on all patients) and refer only chronically treated subjects for ophthamologic (or optometric) consultation. This way, only those subjects who are successfully treated with quetiapine, will have to undergo these more extensive, and expensive examinations.

On the other side of the clinical equation lies the question of relative efficacies among these compounds. For individuals who are resistant to conventional antipsychotic medication, such as haloperidol, clozapine is the most powerful medication. Clozapine also appears remarkably better than conventional medications in moderately refractory individuals. Among the other three compounds, only risperidone has shown therapeutic power superior to conventional medications in such groups. In treatment-responsive groups, both risperidone and olanzapine (but not quetiapine) appear superior to conventional drugs. A few studies have compared risperidone to olanzapine. These data suggest similar effectiveness, but, as mentioned above, somewhat different side effects.

In summary, these newer antipsychotic compounds, while clearly of lower extrapyramidal toxicity than their conventional counterparts, have other contraindications. The patients' specific clinical scenario must guide the clinician in choosing among these drugs. While clozapine is more toxic than the other three compounds, it is also the most powerful antipsychotic treatment available. Thus, when toxicity concerns predominate, clozapine will be a last resort, but when inefficacy is preeminent, clozapine should be tried earlier. Among the other three compounds, quetiapine in general is least toxic, but with the available data, also appears least effective. Choosing between risperidone and olanzapine is usually a choice between different toxicities, as they are equally effective. Olanzapine has more sedation, weight gain, and hepatotoxicity, and is more expensive, while risperidone has greater extrapyramidal and endocrinologic toxicity. Future studies should help delineate differences amongst the atypical drugs, allowing clinicians to better assign priority for use of the drugs in various clinical circumstances.

WILLIAM C. WIRSHING, MD
Los Angeles, California

REFERENCES

Brecher M, Titusville N, Janssen Research Foundation, Clyde C, the Risperidone Study Group. Risperidone in the treatment of psychosis and aggressive behavior in patients with dementia. Presented at the 8th Congress of the International Psychogeriatric Association (IPA); 1997 Aug 17–22; Jerusalem, Israel

ADVISORY PANEL TO THE SECTION ON PSYCHIATRY

MAURICE RAPPAPORT, MD
Advisory Panel Chair
CMA Council on Scientific Affairs Representative
San Jose

THOMAS J. BRADY, MD
CMA Section Chair
San Francisco

BARTON J. BLINDER, MD
CMA Section Secretary
Newport Beach

FRED B. TOMLINSON, MD
CMA Section Assistant Secretary
Santa Cruz

ROGER P. FRIEDENTHAL, MD
Immediate Past Panel Chair
San Francisco

ALAN F. SCHATZBERG, MD,
Stanford University

THOMAS F. ANDERS, MD
University of California, Davis

SIU TANG, MD
University of California, Irvine

ROBERT O. PASNAU, MD
University of California, Los Angeles

LEWIS L. JUDD, MD
University of California, San Diego

CRAIG VAN DYKE, MD
University of California, San Francisco

GEORGE SIMPSON, MD
University of Southern California

RENEE BINDER, MD
Northern California Psychiatric Society
San Francisco

LESTER GOLDSTEIN, MD
Orange County Psychiatric Society
Huntington Beach

STEPHEN HEIDEL, MD
San Diego Society of Psychiatric Physicians
San Diego

MICHAEL GALES, MD
Southern California Psychiatric Society
Los Angeles

BARBARA GARD
Invited Guest
Sacramento

KATHRYN DUKE
CMA Staff
San Francisco

BRENDA SOLORZANO
CMA Staff
San Francisco

LESLIE BIRNBAUM
CMA Staff
San Francisco

Alerts, Notices, and Case Reports

Perils and Pitfalls in the Diagnosis of Cushing's Syndrome

KEH-CHUAN LOH, MRCP
Singapore, Republic of Singapore
PAUL A. FITZGERALD, MD
THEODORE R. MILLER, MD
J. BLAKE TYRRELL, MD
San Francisco, California

SPONTANEOUS CUSHING'S SYNDROME may be corticotropin-dependent due to either pituitary or ectopic hypersecretion of corticotropin, or corticotropin-independent due to primary adrenal neoplasms or nodular hyperplasia.[1] Cushing's syndrome due to pituitary or ectopic corticotropin secretion can be clinically and biochemically indistinguishable.[1,2] In recent years, advances in diagnostic imaging have led to the use of magnetic resonance imaging (MRI)[3,4] and selective venous sampling for corticotropin[5,6] as the principal tools for identifying the source of corticotropin hypersecretion. These ultrasensitive imaging techniques can be misleading, however, if their results are not interpreted with caution, as illustrated in this case report.

Report of a Case

The patient, a 68-year-old nonsmoking woman, had a four-month history of progressive weight gain, central obesity, muscle weakness, and pedal edema. She had been well before being seen, except for long-standing essential hypertension, controlled with the use of atenolol, 50 mg a day. Her initial laboratory evaluation showed hypokalemia (serum potassium level, 2.1 mmol per liter) and fasting hyperglycemia. The initial diagnosis of corticotropin-dependent Cushing's syndrome was based on the following test results: urinary 17-hydroxycorticosteroid excretion, 59.6 µmol per day (21.6 mg per day) (reference range, 5.5-22 µmol per day [2-8 mg per day]); random serum cortisol level, 1,242 nmol per liter (45 µg per dl) (reference range, 190-690 nmol per liter [7-25 µg per dl]); and plasma corticotropin level, 24.7 pmol per liter (112 pg per ml) (reference range, 2.0-11.5 pmol per liter [9-52 pg per ml]). An MRI of the pituitary gland was reported to show a 7×5-mm pituitary microadenoma. She was treated with a regimen of ketoconazole, 400 mg twice a day; spironolactone, furosemide, potassium supplements, and glyburide and referred to our institution for planned pituitary microsurgery.

On physical examination, the patient weighed 105 kg and was 157 cm tall; her blood pressure was 190/100 mm of mercury, and she had a regular heart rate of 66 beats per minute (while taking β-blockade medication). The patient had the typical appearance of Cushing's syndrome with moon facies, dorsocervical and supraclavicular fat pads, and truncal obesity. Additional findings included skin hyperpigmentation, proximal muscle weakness, and pedal edema.

The original sellar MRI was reviewed and found to be inconclusive, and a second study showed a normal pituitary gland. The patient subsequently underwent selective venous sampling from the cavernous sinuses (CS) and the inferior petrosal sinuses (IPS) to test for the central-to-peripheral (P) corticotropin gradient. This demonstrated a maximal CS:P ratio of 2.15 and an IPS:P ratio of 1.38. In view of these equivocal results, an ectopic source of corticotropin secretion was considered. Surprisingly, computed tomography (CT) of the chest revealed a solitary 4×4×5-cm mass in the posterior segment of the right upper lobe, with probable right hilar lymphadenopathy (Figure 1). A CT scan of the abdomen showed hyperplastic adrenal glands but otherwise no abnormalities. An overnight high-dose (8-mg) dexamethasone-suppression test was performed, and her serum cortisol level declined insignificantly from a basal value of 1,465 nmol per liter (53.1 µg per dl) to 1,335 nmol per liter (48.4 µg per dl), a result compatible with ectopic-corticotropin syndrome.

The patient underwent a total resection of the right pulmonary mass with right upper lobectomy. Intraoperatively, the mass was thought to be a probable carcinoma, and gross sectioning revealed a firm, 4.5-cm, poorly circumscribed, tan-pink mass with focal areas of hemorrhage and cavitation. The final histologic examination, however, did not show neoplasm, and staining studies showed numerous branching, beaded, gram-positive, weakly acid-fast, filamentous organisms, consistent with infection with *Nocardia* species (Figure 2). On examination of resected paratracheal and hilar lymph nodes, no neoplasm or microorganism was found. The patient had no evidence of systemic nocardiosis, as indicated by negative culture results from her blood and other sources. Following her chest surgical procedure, she had persistent hypercortisolemia, with random serum cortisol levels ranging from 1,352 to 1,876 nmol per liter

(Loh KC, Fitzgerald PA, Miller TR, Tyrrell JB. Perils and pitfalls in the diagnosis of Cushing's syndrome. West J Med 1998; 169:46–50)

From the Division of Endocrinology, Department of Medicine and Metabolic Research Unit (Drs Loh, Fitzgerald, and Tyrrell), and the Department of Pathology (Dr Miller), University of California San Francisco School of Medicine.

Dr Loh is now with the Endocrine Unit, Department of General Medicine, Tan Tock Seng Hospital, Singapore.

Reprint requests to Keh-Chuan Loh, MRCP, Endocrine Unit, Dept of General Medicine, Tan Tock Seng Hospital, Moulmein Rd, Singapore 308433, Republic of Singapore (e-mail: keh_chuan_loh@notes.ttsh.gov.sg).

ABBREVIATIONS USED IN TEXT

CS = cavernous sinus
CT = computed tomographic
IPS = inferior petrosal sinus
MRI = magnetic resonance imaging
oCRH = ovine corticotropin-releasing hormone
P = peripheral

(49-68 µg per dl). Metyrapone tartrate, 250 mg four times a day, was added to her adrenostatic regimen. She was also given the combination of trimethoprim and sulfamethoxazole for the treatment of nocardia infection.

A renewed search for pituitary Cushing's disease was prompted by the initial surgical failure. She had another pituitary MRI, this time with the use of dynamic perfusion study with gadolinium enhancement because this was thought to improve its sensitivity for detecting small lesions. The early perfusion sequence showed a punctate focus of decreased enhancement in the inferior aspect of the gland, suggestive of a 1.7-mm pituitary microadenoma (Figure 3). This kindled further enthusiasm to search for a pituitary lesion, and another selective venous sampling for corticotropin was performed with ovine corticotropin-releasing hormone (oCRH) stimulation, giving a peak stimulated CS:P corticotropin ratio of 2.87. Despite these equivocal results, a decision was made to proceed with pituitary microsurgery, which was performed three weeks after her thoracotomy. A total hypophysectomy was performed because no focal abnormality was detected, but this failed to disclose a pituitary adenoma or to improve her postoperative plasma cortisol levels. She required levothyroxine sodium, estrogen replacement, and temporary desmopressin acetate administration for her surgically acquired hypopituitarism.

Because hypercortisolism persisted after the hypophysectomy, an ectopic source of corticotropin production was evidently present in this patient. An MRI of the chest and upper abdomen was repeated with dynamic perfusion study to increase its sensitivity for tumor localization. The chest study showed normal findings, whereas the rapid-sequence MRI of the upper abdomen demonstrated a 1-cm area of high signal intensity in the midbody of the pancreas. The lesion was reported to be vascular due to gadolinium enhancement and considered compatible with a carcinoid or islet cell tumor. This was felt to be the source of corticotropin production, and thus resection of the pancreatic mass was planned, with simultaneous bilateral adrenalectomy if the probability of cure from pancreatic resection was thought to be low. The patient underwent her third surgical procedure two weeks after the hypophysectomy and just over a month from her first operation in the pursuit of the cause of her Cushing's syndrome. Intraoperatively, a cyst was found within her pancreas, and excisional biopsy with frozen section failed to show any evidence of tumor; thus, bilateral adrenalectomy was done. Her postoperative course was complicated by pancreatitis with pancreatic pseudocyst formation, which resolved with percutaneous drainage.

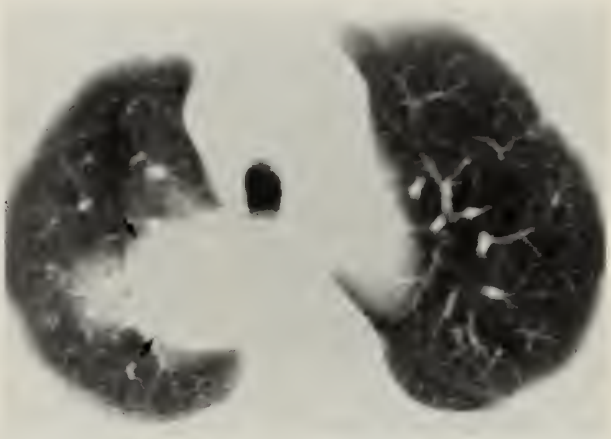


Figure 1.—An axial computed tomographic scan through the lung photographed on lung windows demonstrates a mass lesion emanating from the right paraspinus area (arrows). Resection revealed a nocardial abscess.

After the bilateral adrenalectomy, the patient's serum cortisol levels fell to 55 to 83 nmol per liter (2-3 µg per dl) whereas her plasma corticotropin levels remained high at 11.0 to 27.5 pmol per liter (50-125 pg per ml). Further pursuit of the source of ectopic corticotropin secretion using indium In 111 pentetreotide whole-body scintigraphy again failed to elicit the source. Nevertheless, the hypokalemia and hyperglycemia resolved, and the patient had improvement in hypertension control. She was able to discontinue her adrenostatic drugs, although requiring a regimen of prednisone, 30 mg a day (with a gradual taper to a replacement dosage), and fludrocortisone acetate, 0.1 mg a day.

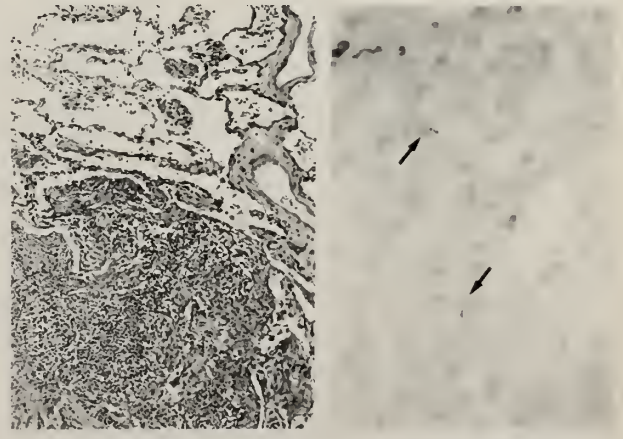


Figure 2.—Photomicrographs of the resected pulmonary lesion: Left, A specimen of lung tissue is shown, with the lower portion demonstrating acute inflammation and necrosis (hematoxylin and eosin stain, original magnification ×20). Right, Arrows show examples of the slender, branching, filamentous forms of Nocardia species (Gram's stain, original magnification ×200).

Figure 3.—Coronal dynamic pituitary magnetic resonance scan: A T1-weighted coronal scan obtained during the infusion of gadolinium pentetate demonstrates a focal hypointense lesion (arrow) at the floor of the sellar just to the right of the midline.

Discussion

The occult ectopic-corticotropin syndrome represents an important form of spontaneous hypercortisolism that is often clinically indistinguishable from pituitary-dependent Cushing's disease.[1,2] This case exemplifies the perils and pitfalls of current imaging techniques in the differential diagnosis of corticotropin-dependent hypercortisolism. Despite the greater reliance on these sophisticated tools, certain clinical or biochemical features are helpful clues to differentiate between pituitary-dependent and ectopic Cushing's syndrome.[7–9] As illustrated by this case, features such as a relatively rapid onset of symptoms, substantial muscle weakness, skin hyperpigmentation, edema, hypertension, and spontaneous hypokalemia are all more commonly associated with ectopic Cushing's syndrome. In reviewing all reported cases of bronchial carcinoid with ectopic corticotropin production, Leinung and co-workers[8] found that 69 of 74 patients (93%) had clinical manifestations consistent with typical Cushing's disease; however, hypokalemia (serum potassium level, <3.3 mmol per liter) occurred in 41 of 59 of patients (69%) as compared to less than 10% in patients with a pituitary source from another series.[9] In a review of 16 patients with ectopic corticotropin secretion, Howlett and colleagues found hypokalemia in all patients, including a subgroup of 10 patients with occult tumors (although 2 patients were taking potassium-losing diuretics).[9] Proximal myopathy was also noted in all their patients with occult tumors.

Hormonal studies often fail to differentiate clearly between the pituitary and ectopic sources of corticotropin secretion because of considerable overlap of test results, including pharmacologic testing such as the dexamethasone-suppression test, the metyrapone stimulation test, and the oCRH stimulation test.[2,7] In our patient, however, results from the pharmacologic study were consistent with the diagnosis of ectopic corticotropin secretion, as her cortisol level remained nonsuppressible after high doses of dexamethasone were administered.

Many investigators have relied directly on MRI of the pituitary gland or selective venous sampling for corticotropin (or both) in the diagnostic evaluation of corticotropin-dependent hypercortisolism.[3–6] The accuracy of pituitary imaging to distinguish Cushing's disease from ectopic corticotropin secretion is limited by the relatively high incidence of incidental pituitary microadenomas in the normal population, as reported in as many as 20% of adults.[10,11] This is further confounded by the fact that pituitary corticotropic adenomas are often less than 5 mm in size, and as many as 50% may be undetectable on MRI.[7] Although the presence of a pituitary lesion in our patient was not convincingly demonstrated by the conventional sellar MRI, a subsequent dynamic-flow study with gadolinium contrast, a technique that enhances the detection of pituitary microadenomas by assessing the differential time lag in contrast enhancement between tumoral and normal pituitary tissue,[12] showed unequivocally the presence of a tiny intrapituitary lesion. Transsphenoidal surgical procedure, however, neither revealed a corticotropic adenoma nor resulted in a cure for our patient, indicating that dynamic-flow MRI may be subject to artifacts, with compromised specificity. Unexpectedly, the result of dynamic-flow MRI of the pancreas was again erroneous, leading to an inappropriate pancreatic operation.

Selective venous sampling for corticotropin from bilateral IPS has been widely regarded as the most accurate method for differentiating between pituitary-dependent Cushing's disease and ectopic Cushing's syndrome.[2,5–7] Doppman and associates performed selective venous sampling for corticotropin from bilateral IPS in a large series of patients from the National Institutes of Health and found no false-positive results in identifying Cushing's disease in basal specimens when the IPS:P corticotropin ratio was 2 or higher. After oCRH stimulation, they found that a peak IPS:P corticotropin ratio of 3 or higher identified all patients with Cushing's disease with no false-positive results, indicating 100% sensitivity and specificity.[6] Superselective venous sampling from bilateral CS, developed by Teramoto and colleagues, has been reliable in diagnosing Cushing's disease, if the CS:P corticotropin gradient is greater than 10, without the need for oCRH stimulation.[13] Because of poor availability of oCRH until recently, superselective venous sampling from bilateral CS is being used in our center because this has shown improved diagnostic accuracy. Patients must have hypercortisolemia at the time of sampling, however, for the study to be valid because false-positive results have been reported in patients with ectopic corticotropin secretion who manifest periodic hormonogenesis.[14]

Superselective venous sampling for corticotropin did not resolve the diagnostic dilemma in this case because the results were equivocal. There have been substantial

differences in the central-to-peripheral corticotropin ratios used by different investigators to distinguish pituitary from ectopic sources of corticotropin. Following the more recent National Institutes of Health data,[15] which apply similar cutoff values for corticotropin sampling from either IPS or CS, the initial unstimulated CS:P corticotropin ratio (2.15) could be considered positive for a pituitary source of corticotropin secretion in this patient. Conversely, this gradient is grossly inadequate for locating a pituitary source of corticotropin secretion if the criteria from Teramoto and co-workers are followed (discussed earlier).[13] The interpretation of corticotropin ratios after oCRH stimulation can likewise be difficult: a similar IPS:P corticotropin ratio of greater than 2 is used by Findling and associates for sampling before or after oCRH stimulation,[16] whereas other investigators use a higher cutoff for ratios after oCRH stimulation.[6,15,17] This case illustrates the subtleties involved in interpreting selective venous sampling results, especially when borderline values occur. The different criteria used to differentiate between pituitary and ectopic corticotropin production are likely due to several factors such as sampling techniques and accuracy, methods of corticotropin measurement, and patient variations. Because this is a highly technical procedure, the use of selective venous sampling is best confined to a few specialized centers that have sufficient experience to provide their own diagnostic criteria.

Because most lesions from occult ectopic-corticotropin syndrome are in the thorax, CT or MRI of the chest is usually performed as part of the diagnostic evaluation.[7–9] Unexpectedly, the lesion detected on chest CT scan represented a false-positive finding in this case, proving histologically to be pulmonary nocardiosis. This illustrates that the cause of pulmonary mass lesions in patients with Cushing's syndrome may not be clinically evident. Biopsy of all such lesions is indicated because a tissue diagnosis is essential to guide management. In a review of 23 patients with endogenous Cushing's syndrome (most of whom had ectopic-corticotropin syndrome) and opportunistic infections, nocardiosis, as occurred in our patient, along with cryptococcosis, aspergillosis, and *Pneumocystis carinii* pneumonia, constituted the predominant conditions.[18] Manifestations of infections in such patients are often masked by the hypercortisolism, as was the case in our patient.

Because many neuroendocrine tumors may express somatostatin receptors, radiolabeled somatostatin analogue scintigraphy has been introduced for tumor localization. This has been promoted as a new investigative tool in patients with suspected ectopic-corticotropin syndrome because eutopic corticotropic pituitary adenomas do not usually express somatostatin receptors.[19] In vivo scintigraphy with In 111pentetreotide, however, failed to show any abnormal uptake in our patient. Although lacking published data, our institutional experience thus far has indicated disappointing results in the use of pentetreotide scan to locate "occult" ectopic-corticotropin tumors.

In cases wherein the source of corticotropin-dependent Cushing's syndrome cannot be identified, bilateral adrenalectomy should be considered early to initiate prompt and effective control of hypercortisolism. Because of recent advances in laparoscopic surgery, patients can now undergo bilateral adrenalectomy with minimal morbidity and a shortened hospital stay.[20] Conversely, medical adrenal blockade with ketoconazole, metyrapone, or aminoglutethimide commonly fails to achieve satisfactory control of hypercortisolism.[21,22] Our patient showed remarkable improvement in her metabolic status after bilateral adrenalectomy, with the successful withdrawal of antiadrenal drugs, hypoglycemic agents, diuretics, and potassium supplements.

REFERENCES

1. Miller WL, Tyrrell JB. The adrenal cortex. chap 12. In: Felig P, Baxter JD, Frohman LA, editors. Endocrinology and metabolism. 3rd ed. New York (NY): McGraw-Hill; 1995, pp 659–678

2. Findling JW. Eutopic or ectopic adrenocorticotropic hormone-dependent Cushing's syndrome? A diagnostic dilemma (editorial). Mayo Clin Proc 1990; 65:1377–1380

3. Doppman JL, Frank JA, Dwyer AJ, Oldfield EH, Miller DL, Nieman LK, et al. Gadolinium DTPA enhanced MR imaging of ACTH-secreting microadenomas of the pituitary gland. J Comput Assist Tomogr 1988; 12:728–735

4. Peck WW, Dillon WP, Norman D, Newton TH, Wilson CB. High-resolution MR imaging of pituitary microadenoma at 1.5 T: experience with Cushing disease. AJR Am J Roentgenol 1989; 152:145–151

5. Findling JW, Aron DC, Tyrrell JB, Shinsako JH, Fitzgerald PA, Norman D, et al. Selective venous sampling for ACTH in Cushing's syndrome: differentiation between Cushing disease and the ectopic ACTH syndrome. Ann Intern Med 1981; 94:647–652

6. Oldfield EH, Doppman JL, Nieman LK, Chrousos GP, Miller DL, Katz DA, et al. Petrosal sinus sampling with and without corticotropin-releasing hormone for the differential diagnosis of Cushing's syndrome. N Engl J Med 1991; 325:897–905

7. Wajchenberg BL, Mendonca BB, Liberman B, Adelaide M, Pereira MA, Kirschner MA. Ectopic ACTH syndrome. J Steroid Biochem Mol Biol 1995; 53:139–151

8. Leinung MC, Young WF Jr, Whitaker MD, Scheithauer BW, Trastek VF, Kvols LK. Diagnosis of corticotropin-producing bronchial carcinoid tumors causing Cushing's syndrome. Mayo Clin Proc 1990; 65:1314–1321

9. Howlett TA, Drury PL, Perry L, Doniach I, Rees LH, Besser GM. Diagnosis and management of ACTH-dependent Cushing's syndrome: comparison of the features in ectopic and pituitary ACTH production. Clin Endocrinol 1986; 24:699–713

10. Molitch ME, Russell EJ. The pituitary 'incidentaloma.' Ann Intern Med 1990; 112:925–931

11. Hall WA, Luciano MG, Doppman JL, Patronas NJ, Oldfield EH. Pituitary magnetic resonance imaging in normal human volunteers: occult adenomas in the general population. Ann Intern Med 1994; 120:817–820

12. Stadnik T, Spruyt D, van Binst A, Luypaert R, d'Haens J, Osteaux M. Pituitary microadenomas: diagnosis with dynamic serial CT, conventional CT and T1-weighted MR imaging before and after injection of gadolinium. Eur J Radiol 1994; 18:191–198

13. Teramoto A, Nemoto S, Takakura K, Sasaki Y, Machida T. Selective venous sampling directly from cavernous sinus in Cushing's syndrome. J Clin Endocrinol Metab 1993; 76:637–641

14. Yamamoto Y, Davis DH, Nippoldt TB, Young WF Jr, Huston J III, Parisi JE. False-positive inferior petrosal sinus sampling in the diagnosis of Cushing's disease. J Neurosurg 1995; 83:1087–1091

15. Doppman JL, Nieman LK, Chang R, Yanovski J, Cutler GB Jr, Chrousos GP, et al. Selective venous sampling from the cavernous sinuses is not a more reliable technique than sampling from the inferior petrosal sinuses in Cushing's syndrome. J Clin Endocrinol Metab 1995; 80:2485–2489

16. Findling JW, Kehoe ME, Shaker JL, Raff H. Routine inferior petrosal sinus sampling in the differential diagnosis of adrenocorticotropin (ACTH)-dependent Cushing's syndrome: early recognition of the occult ectopic ACTH syndrome. J Clin Endocrinol Metab 1991; 73:408–413

17. Tabarin A, Greselle JF, San-Galli F, Leprat F, Caille JM, Latapie JL, et al. Usefulness of the corticotropin-releasing hormone test during bilateral inferior petrosal sinus sampling for the diagnosis of Cushing's disease. J Clin Endocrinol Metab 1991; 73:53–59

18. Graham BS, Tucker WS. Opportunistic infections in endogenous Cushing's syndrome. Ann Intern Med 1984; 101:334–338

19. de Herder WW, Krenning EP, Malchoff CD, Hofland LJ, Reubi JC, Kwekkaboom DJ, et al. Somatostatin receptor scintigraphy: its value in tumor localization in patients with Cushing's syndrome caused by ectopic corticotropin or corticotropin-releasing hormone secretion. Am J Med 1994; 96:305–312

20. Ferrer FA, MacGillivray DC, Malchoff CD, Albala DM, Shichman SJ. Bilateral laparoscopic adrenalectomy for adrenocorticotropic dependent Cushing's syndrome. J Urol 1997; 157:16–18

21. Tabarin A, Navarranne A, Guerin J, Corcuff JB, Parneix M, Roger P. Use of ketoconazole in the treatment of Cushing's disease and ectopic ACTH syndrome. Clin Endocrinol 1991; 34:63–70

22. Engelhardt D, Weber MM. Therapy of Cushing's syndrome with steroid biosynthesis inhibitors. J Steroid Biochem Mol Biol 1994; 49:261–267

Commentary

In Search of the Fourth Maxim

JOHN W. GARDNER, PhD, *Stanford, California*

John W. Gardner has been a public servant since his days with the Federal Communications Commission and the Marine Corps during World War II. His posts have included President of the Carnegie Corporation and Carnegie Foundation for the Advancement of Teaching; Secretary of Health, Education and Welfare during the Johnson Administration; founder of the citizens' lobby, Common Cause, and founder of a leading organization in the voluntary sector, Independent Sector. He has been appointed to commissions and task forces by four presidents. His work is fueled by high energy, unwavering optimism and confidence in the ability of the American people to right what is wrong. His carefully chosen words have helped build groups, neighborhoods, hamlets and cities into thriving communities.

Dr. Gardner is a scholar and activist, eager to learn from many sources and willing to take on tough challenges. He persuades by the power of his intellect and his warmth. Family, friends, colleagues and strangers write to and visit him constantly, seeking wisdom and encouragement. He gives liberally and transmits the spark of renewal.

The Commentary we are publishing in this issue of the WESTERN JOURNAL OF MEDICINE *grew from John Gardner's reflections, from his curiosity, and from an informal research project. I predict that it will be engaging, instructive and provocative—like the author.*

LINDA HAWES CLEVER, MD
Editor

On a quiet summer day 22 years ago, I began the train of thought that led eventually to the search for the Fourth Maxim.

For many years I had collected proverbs, and on that day I was thinking about the remarkable brevity of some of the greatest folk sayings.

There are many memorable ones that are no longer than four words. As every student of proverbs knows, the four-worders often rely on the use of balance, contrast and repetition: "Soon ripe, soon rotten," "Easy come, easy go," "Young saint, old sinner."

There are not so many three-word proverbs, but everyone can remember a few: "Misery loves company," "Love is blind," "Make haste slowly," "Que sera, sera," Some of these are thousands of years old. If you don't find yourself impressed with that fact, try making up a three-word saying that is memorable enough to last a week.

The two-word proverbs are the aristocrats of verbal brevity, and as befits aristocrats they favor the imperative mood. There are declarative two-worders ("Power corrupts," "Tempus fugit") but most of the two word proverbs tell us what to do or how to live. They are maxims. "Know thyself," is perhaps the most famous.

As I reflected on these terse sayings I asked myself "Why not a one-word maxim?" If "Know thyself" passes muster as a legitimate maxim, why not the single word "Know"? If "Be yourself" is acceptable, why not the single word "Be"?

If you continue in that experimental vein, you soon find that the most plausible one-word maxims are verbs. There are a few nouns used in the spirit of a toast—"Health!" "Fortune!" And the nouns on coats of arms—"Honor," "Veritas." But none of these have the quality of sayings. In contrast, Harry Golden's advice "Enjoy!" seems to me a perfectly appropriate one-word maxim. And like "Know" and "Be," it is a verb in the imperative mood.

If the one-word maxim is most likely to be a verb that instructs us what to do, its value will lie entirely in the soundness of the instruction given. In longer proverbs, ideas of dubious wisdom may be saved by vividness or saltiness of expression. But in one-word proverbs vividness or any other marks of style are impossible. The value of the saying will depend entirely on the meaning of the one word.

With those thoughts firmly in mind, I set out to find the choicest one-word maxims. Over weeks and months I discussed the search with many people. I put the question this way: "Suppose you were allowed to communi-

(Gardner JW. In search of the fourth maxim. West J Med 1998; 169:51–52)

From the School of Education, Stanford University, Stanford, California.
Reprint requests to John W. Gardner, School of Education, Stanford University, Stanford, CA 94305-3084.

cate one word of advice to a young person living in the year 2500. What would it be?"

One word!

The results of the conversations surprised me. It turns out that there are three one-word maxims almost universally nominated for the top of the list. There is not perfect agreement as to the order of the three, so I'll list them in the order that seems appropriate to me.

The First Maxim is "Live!" I am conscious of the moral questions the maxim may arouse (There are fates worse than death, etc.), but the word—and the reality it denotes—still embraces everything else. "Live!" If you have in mind Schweitzer's "reverence for life," and a biologist's sense of the complexity and wonder of the life process, you will recognize that most people who mentioned the word had in mind more than an invitation to hedonism. Live, be, experience, grow, sense, function as a healthy organism! Everything else builds on that.

Of the three maxims most widely agreed on, another was "Learn." Learning begins before birth, and is at the heart of human behavior. It is involved in every significant act we perform.

The third of the three maxims widely agreed on is "Love!" You have discovered by now that we cannot play the game of one-word maxims without allowing each maxim to carry a lot of meanings. "Love" would have to mean many kinds of love—fraternal, sexual, religious, humanistic.

So much for the first three maxims: Live, learn and love. Readers who would like to check the results with friends will find considerable agreement on those three. But when we move beyond that point, we encounter a curious fact: though people tend to agree on the first three maxims, there is nothing approaching consensus on the identity of the fourth.

A fascinating and puzzling fact!

A devout young friend of mine says "Believe!" A scientist friend says "Seek!" A distinguished physician, the late Dr. Russell Lee, said "Produce!" I found no consensus.

Then some years ago I was to give an after-dinner talk to one of the most distinguished scholarly societies in the nation, and I decided to put the question to the assembled members. Where would I find a group of men and women better fitted to assist in the Search for the Fourth Maxim? I described the history of the search, and then supplied them with slips of paper on which to record their nominations.

What were the results?

If we can accept the judgment of this distinguished group, the Fourth Maxim is one or another word centering on the cognitive processes. The group was not unanimous as to what that word would be. The words most often mentioned were:

Think
Understand
Know

If one were to draw from their responses a Fifth Maxim, it would be one or another word from the following cluster:

Give
Help
Serve
Share
Care

And I'm happy to report that their Sixth Maxim would involve a lightening of the hitherto serious mood:

Laugh
Smile
Play
Enjoy

So much for the first six maxims. In my many conversations on the subject I was invariably asked, "What is your own choice for the Fourth Maxim?" My choice would be "Aspire." In some respects I would prefer the homely word "Try," but "Aspire" says more. It says "try for something better." That seems to me the essence of humans at their best.

I won't put my choice ahead of the distinguished scholars I consulted, but I'll take the liberty of ranking "Aspire" as the Seventh Maxim.

The list now goes:

Live
Learn
Love
Think
Give
Laugh
Aspire

One's preference in maxims is of course a highly personal matter. I leave it to the reader to diagnose the two members of the audience who wrote on their slips of paper the word "Don't," and the one member who wrote "Escape!"

Commentary

Invisible Children

ELENA O. NIGHTINGALE, MD, PhD, *Washington, DC, and* KARI HANNIBAL, MA, *Boston, Massachusetts*

Each year several thousand minors without legal immigration documents enter the United States by themselves and are arrested by the Immigration and Naturalization Service (INS). In 1995, the last year for which such data were made available to the *Los Angeles Times* by a spokeswoman for the INS,[1] 2,028 unaccompanied, undocumented juveniles were arrested. As reported previously,[2] these children come from many countries and regions, including China, Haiti, Cuba, and Latin America. Most of these children are placed in foster or a relative's care or deported in a matter of days. If a parent or potential guardian is in the United States illegally, the fear of deportation can preclude their coming forward to claim the child, placing the child in a doubly difficult position. Deportation has become an easier and faster process since April 1, 1997, when the Illegal Immigration Reform and Immigrant Responsibility Act of 1996 went into effect. Now immigration officials at the border can decide to expel immigrants they apprehend, including those seeking asylum, without a hearing and without the right to appeal. This expedited process has the potential for returning undocumented persons and any children with them to hardship, particularly those who are escaping from brutality, abuse, or civil disturbance.

Despite the rapid disposition of most cases of undocumented, unaccompanied minors, each year several hundred such children, some as young as 5 years,[3] are placed in INS custody in a variety of settings, ranging from foster care of varying safety and quality to detention centers or even jails, even though detention is for administrative, and not criminal, offenses. Once in INS detention, a 1997 Human Rights Watch report states, children become "invisible: they have slipped through the cracks in America's legal system."[4(p1)] The Human Rights Watch report documents that although detention should be limited to 30 days,[5] this is not always the case. For example, between October 7 and 14, 1996, 241 children were in long-term detention, 20% of them for more than 4 months.[6] By law, medical care should be provided to detained children. The neglect of the health needs of children in INS detention, however, such as lack of minimal hygienic conditions, immunizations, access to care, and inadequate record keeping, were summarized previously.[2]

Mariaelena, aged 15 years, who had been in detention for more than a year when interviewed in 1996 at Los Padrinos in Los Angeles County by Human Rights Watch, said "If you are bad—if you do not do your exercise or use bad language—they send you to 'the box.' Then you are alone in a room, with nothing." The staff described "the box" as a medical isolation chamber with a metal cot, a sink, a toilet, and no windows.[4] International human rights standards prohibit solitary confinement for children.[4(p48)]

In 1985 a class-action suit was brought against the INS on behalf of Jenny Lisette Flores and other children mistreated and without adequate medical attention, education, or recreation in INS custody. In 1987 a settlement specified that facilities housing minors in INS custody must meet certain standards of housing and care. The settlement was not fully honored, and on January 13,1997, a second settlement was reached.[6,7] Among the requirements, the INS must collect statistical information weekly for all minors in INS custody longer than 72 hours, including biographical data and dates for each placement, removal, or release. Emergency and routine medical care and a complete medical examination, including screening for infectious diseases within 48 hours of admission (excluding weekends and holidays), are also required.[7] An individualized plan of care must be set up for each minor. The facilities for children must be safe and sanitary. We hope that steps toward compliance with the latest agreement are underway.

Rivera and Lindsey describe guidelines for medical care of minors provided by the INS Health Services Division.[8] They also state that minors "are detained only briefly, usually a few hours, at service processing centers." If the detention of these children by the INS were brief, there would be no invisible children. The Human Rights Watch report asserts that conditions in Los Angeles County and Arizona detention centers visited in 1996 "violate the children's rights under international law, the US Constitution, US statutory provisions, INS regulations, and the terms of court orders binding on the INS."[4(p1)] The INS's lack of compliance with the first *Flores* settlement led to the need for a second.[5] Given this evidence, it is apparent that good guidelines are not always followed uniformly.

From the Institute of Medicine, National Research Council, Board on Children, Youth, and Families, Washington, DC (Dr Nightingale), and The Albert Schweitzer Fellowship, Boston, Massachusetts (Ms Hannibal).The affiliations are listed for information purposes only. The contents of this commentary are the sole responsibility of the authors.

Reprint requests to Elena O. Nightingale, MD, PhD, Scholar-in-Residence, Institute of Medicine, National Research Council, Board on Children, Youth, and Families, 2101 Constitution Ave, Washington, DC 20418.

Careful and systematic monitoring of conditions and delivery of services in places of detention is required and mandated. It is not clear, however, that the INS can or should accomplish these tasks. In January 1998, a federal advisory commission recommended that the INS be abolished and its duties assigned to other agencies.[9] Part of the reason is that the INS has potentially conflicting roles of curtailing illegal immigration and providing benefits for legal immigrants. President Clinton is said to prefer reorganization to clarify these roles.[9]

Unaccompanied minors, regardless of how or why they entered the United States, need the intervention and care of adult advocates. The INS responsibility for either or both deporting and detaining undocumented minors and supervising the health, education, and well-being of the minors in their jurisdiction also appears to be conflicting.

Action by the medical community, especially in states with large numbers of immigrants, would help make these unaccompanied, undocumented children both visible and cared for. The medical community could study how to work more closely with the INS to provide health services for minors in INS custody, with responsibility for those services assumed by a health agency and not by the INS, by commonly agreed-on means. Mental health services for these children, many of whom have been seriously traumatized before entering this country, could be beneficial or prevent further trauma. Collaboration between the legal and medical professions could help physicians gain access to places where minors are held because access is often difficult. Independent physician participation in site visits for the purposes of inspecting, monitoring, documenting, and providing services is crucial for protecting the safety and security of the children.

Health professionals could join forces with local or national human rights groups (such as Physicians for Human Rights) to report instances in which they have observed abuse, neglect, or poor provision of health services. Careful documentation and discussion with INS officials would help the INS to identify and correct problems. Physicians and professional organizations such as the American Academy of Pediatrics, which is already active in human rights, could be effective advocates for the early release of youngsters from detention and for placement in appropriately monitored settings. The American Academy of Pediatrics and other medical professional organizations could also be sources of volunteers for site visits or to provide health care.

Immigration and Naturalization Services Commissioner Doris Meissner, by signing the 1997 settlement in the *Flores* case, indicated her willingness to implement the agreement fully, and she is to be commended. Nonetheless, the medical profession has an opportunity now to make a major contribution to rescue these children from obscurity and neglect.

REFERENCES

1. McDonnell PJ. INS adopts reforms on custody of minors. Los Angeles Times April 30, 1997, Vol 116, p B1, col 6

2. Nadeau K, Hannibal K, Sirkin S, Nightingale EO. Immigrating unaccompanied minors—A neglected minority? (Correspondence) West J Med 1997; 166:221

3. Due process. Harvard Law Rev 1993; 107:175–194

4. Human Rights Watch. Slipping Through the Cracks: Unaccompanied Children Detained by the US Immigration and Naturalization Service. New York (NY): Children's Rights Project; 1997

5. Makalusky JM. Reno v. Flores: A violation of international law? N Engl Int Compar Law Annu 1996; 2:1–23

6. Bussiere A. Final settlement in Flores v. Reno offers hope to children in INS custody. Youth Law News 1997 May-Jun, pp 8–10

7. Jenny Lisette Flores, et al, Plaintiffs-vs-Janet Reno, Attorney General of the United States, et al, Defendants. Case No. CV 85-4544-RJK(Px), Stipulated Settlement Agreement (CD Cal 1997) (in press)

8. Rivera AI, Lindsey CL. Immigration and Naturalization Service responds (Correspondence). West J Med 1997; 166:221–222

9. Schmitt E. White House will reject advice to abolish immigration service, officials say. New York Times, Jan 21, 1998, Vol 147, p A14 (N), col 2

Correspondence

Editor's Note: We regret that the following letter from University of California President Richard C. Atkinson was omitted from the May issue, which was dedicated to current issues in medical education and to the Final Report of the Commission on the Future of Medical Education. President Atkinson's response to the Commission's report and accompanying white papers acknowledges their contribution as a useful informational resource for those engaged in the ongoing debate regarding future directions in medical education.

January 27, 1998

Thomas Langfitt, MD
Chairman
Commission on the Future of Medical Education

Charles B. Wilson, MD
Executive Director
Commission on the Future of Medical Education

Dear Tom and Charlie:

I wish to take this opportunity to express my thanks to you and to the members of the Commission on the Future of Medical Education for their intensive deliberations and contributions that led to the Commission's final report and the associated collection of "white papers."

I was pleased to see that the report covered all the areas that I asked the commission to address. The background papers prepared and selected for the commission by the UCSF Center for the Health Professions and Commission staff were particularly useful in their analyses of health system changes and related workforce and educational implications. While there will not be universal agreement, either within the University of California or among national experts, on the specific policy conclusions reached by some of these analysts, the papers are nevertheless stimulating and useful. In addition, the report provides an informative discussion of many current issues in medical education.

It is an ambitious and wide-ranging document that attempts to diagnose the current trends and problems in contemporary academic medical centers in the UC system and, by extension, across the nation. I note that many of the principles and recommendations discussed in the report are broadly supported within the University community, e.g., strengthening continuity between medical undergraduate and graduate education curriculum, expanding outreach efforts to ensure diversity in medical education and the future physician workforce, defining core clinical competencies, pursuing systemwide efforts to evaluate medical education costs and viable options to support these costs, and periodically examining University health sciences enrollments in light of workforce needs, market trends, and related variables. I was also pleased to note that many of the report's recommendations concerning educational programs and related curricular initiatives are already in place within the University's five Schools of Medicine.

This report makes a strong contribution to the ongoing discussion and debate on current issues and future directions in medical education. I anticipate that the report will be used as an important informational resource to those responsible for academic planning at our individual medical schools, and at the universitywide level as we attempt to integrate our academic, patient care, and research missions.

On behalf of the University of California community, I am happy to convey our sincere appreciation to you and to the members of the commission for your contributions to this major undertaking.

Sincerely,

(signed) Richard C. Atkinson
President

cc: Provost King
Vice President Hopper
Vice President Gurtner

Lessons From the Practice

That Funny Feeling

WILLIAM E. BYRD, MD, *Roanoke Rapids, North Carolina*

Things are seldom what they seem.
Skim milk masquerades as cream.
—W.S. Gilbert, H.M.S. Pinafore

Although this happened some years ago, I can still remember it as if it happened last weekend. Mildred Watson had never requested to see me on an urgent basis. Her only medical problems, a hiatal hernia with reflux and bilateral subacromial bursitis of the shoulders, had been well controlled with medications for over ten years; hence, her call was both surprising and unsettling.

Mildred was 44, had never married, and cared for a 30 year old brother who had sustained brain damage in a hit and run auto accident in his early 20's. Sadly, her parents had drowned seven years before when their fishing boat capsized in a thunderstorm 200 yards off the eastern shore of Virginia.

Shortly after 4:00 PM on a cool Friday November afternoon, Mildred called the clinic. I was finishing up some paper work and dictations, hoping to leave early to attend one of my alma mater's basketball games, some 80 miles away. My nurse, Carol, screened the call and came back to my office.

"It's Mildred Watson," she said.

"What's up?" I asked.

"She said she just feels funny. She never felt like this before."

"What kind of funny?" I inquired. "Fever, chills, headache, pain, lightheadedness?"

"No," Carol replied. "She says she's just worried because she's never felt like this before."

Sighing, while quickly looking at my watch, I said, "Then tell her to come right away; but I need to be on the road in an hour."

Mildred was in my office in twenty minutes. Her vital signs, including temperature, were normal. I immediately began to take the history, hoping her problem could be resolved in five to ten minutes. "Tell me what's bothering you, Mildred."

"I don't know if I can explain it right, but it seems as if I'm here and my body's over in the corner," she replied hesitantly.

Thinking this might be some type of depersonalization, I said, "Have you been under any unusual stress?"

"Oh, no," she replied. "Actually things have been going rather well. Tommy's doing fine," she continued. "Luckily he has had no urinary tract infections in over two months." Becoming more serious, she said, "You must think I'm a flake, but for the past twenty-four hours I've been in some kind of trance." Laughing she said, "And I can't afford to do drugs."

Smiling faintly, I replied, "I know. Tagamet and Ibuprofen shouldn't give anyone a high." Then trying to pick up the pace, I asked, "Any headache, fever, blurring of vision, difficulty speaking, stiffness of the neck?"

"No," she replied. "I really don't even feel sick - which is in a way what makes me so worried."

Glancing at my watch, I said, "Why don't I let Carol get you in a gown, and we'll see if we can quickly sort this out."

Mildred's brief physical exam, including an abbreviated neurologic evaluation, was entirely normal. I must have appeared puzzled for Mildred asked, "What do you think is going on? I can assure you I'm not mental."

Staring into the distance for a moment, straining for a differential diagnosis of Mildred's symptoms, I methodically replied, "No, of course not." Then, turning toward Mildred, I said, "I'm really not sure, Mildred, but I don't think it's anything serious."

It was now 5:00 PM, and I was faced with a monumental judgment call. I could have Mildred come back Monday for followup, or I could admit her for evaluation. I really had no reason for admission. I would have to embellish the history and physical for her to pass the precertification criteria of her health plan.

Recovering, I said, "Mildred, I'm going to admit you to the hospital for an overnight stay, get an MRI scan of the brain and have the neurologist see you."

Immediately straightening her neck and tensing her shoulders, she said, "Do you think I have a brain tumor?"

"No, no, of course not," I replied. "Your symptoms have come on too suddenly. In fact, it doesn't even sound like a seizure or transient ischemic attack. But I think we need to check things out since you've never had anything like this before. If everything is normal, then you can go home in the morning."

I admitted Mildred for overnight observation and called Frank Starling, the neurologist on call for the

(Byrd WE. That Funny Feeling. West J Med 1998; 169:56–57)

From Roanoke Valley Internal Medicine and Rheumatology, Roanoke Rapids, North Carolina.
Reprint requests to William E. Byrd, MD, Roanoke Valley Internal Medicine and Rheumatology, 1724 East 10th St, Roanoke Rapids, NC 27870.

weekend. "Frank," I said, "I'm not sure what's going on with Mildred Watson, but I would appreciate it if you would take a look at her this evening. I have already ordered an MRI scan of the brain. If you don't find anything, I'll let her go in the morning. I'm leaving shortly for the State game but should be back by midnight. Call me if you find anything earth-shattering."

"No problem," Frank Starling replied. "If you don't hear from me you can assume everything was normal."

At 12:15 AM I returned to find a message on my answering machine from Frank Starling. He was still at the hospital when I got hold of him.

"Incredible call, John."

"What do you mean?" I stammered.

"We just finished the angiogram. Mildred Watson has the biggest anterior communicating artery aneurysm I've ever seen. Her LP was clean, and we're getting ready to fly her out to the university for further management. I'm glad you didn't send her home," he continued.

"I'm glad, too," I replied, momentarily dazed. "But what did you think of her symptoms? Did they suggest aneurysm to you?"

"Oh, good Lord, no. I didn't know what to make of her out-of-body experience, but that's beside the point. We made the diagnosis, and you saved her life, pal. Congratulations."

Still stunned, I said, "Absolutely amazing. Thanks for your help. I'll talk to you tomorrow."

"You bet."

Mildred Watson's aneurysm was clipped uneventfully at the university the following day and within a week she returned home without any neurologic deficit.

In the years following her death at 47 in an auto accident, I become chilled when I think of how a little carelessness, or a little selfishness in not wanting to be delayed, could have given me a lifetime to regret a preventable medical catastrophe. I am continually humbled by the sequence of events. Probably the only reason I hospitalized Mildred was the complete change in the pattern of her usual symptoms. I certainly could offer no meaningful differential diagnosis, and I never felt that she had anything that was life-threatening. Someone must have been watching over the both of us. I made the right decision for the wrong reasons.

Lessons From the Practice

Focus on the Medical History

MURTHY V.S. ANDAVOLU, MD, *Arcadia, California*

As a medical resident on call late one night, I admitted a patient from the Emergency Room (ER) for "observation following head trauma." A 35-year-old, previously healthy gentleman had tripped and fallen off the stairs at his home, resulting in soft tissue trauma to the side of his head. He did not have any headache, dizziness, nausea, vomiting or visual disturbances following the fall, but he was concerned and came to the ER to be cleared by a physician. The ER physician did not note any evidence of external injury but noticed a dilated pupil in his right eye. A computerized tomographic (CT) scan of the head was done and was normal. An emergency consultation by the neurologist was requested. The neurologist on call advised over the phone that the patient be admitted to the hospital for observation. The ER physician told the patient and his wife that bleeding inside his head could not be ruled out and that he was at risk of dying from an unrecognized bleed into the head if he was not watched carefully over the next 24 to 48 hours. The young couple was terrified. The sobbing wife left as her husband was admitted to the hospital.

On admission to the ward, I examined the patient in detail and found him to be anxious but hemodynamically and neurologically stable, with no evidence of external injuries. The only abnormal finding on examination was a mildly dilated right pupil that was irregular with ragged margins, reacting sluggishly to light. On noting the unusual appearance of the pupil, I asked him if he had ever had any surgery on the eye. He replied that about seven years before, he had been involved in a motor vehicle accident in his home country, at which time he had injured his right eye and bled into the anterior chamber, and that surgery had had to be performed to evacuate the blood and to release adhesions around the pupil. I asked the patient if he had given this piece of history to the doctors in the ER. He replied that no one had asked him such a question and that he had not considered it relevant enough to volunteer the information.

A patient with pupillary irregularity due to prior surgery had been admitted with a diagnosis of possible intracranial bleed! And the worst was yet to come. The patient's wife, after a very anxious, sleepless night at home, arrived at the hospital early the next morning. The patient was in the bathroom at the time. Finding his bed empty, she broke out crying, for she thought her husband had died—thanks to all the "education" she had received in the ER about the possible consequences of head injury.

This experience taught me that obtaining a detailed and well-directed history and physical examination helps not only in making a right diagnosis, but also prevents costly mistakes. The practice of asking all relevant questions in the history and correlating the answers with the physical findings forms the basis of diagnostic decision-making. It is then reasonable to order the relevant diagnostic tests to confirm or rule out the clinical suspicion(s). The sequence of these events must never be changed.

I also learned about the powerful impact our statements can make on the minds of our patients and their relatives. These statements can have far-reaching ethical and legal implications. Realization of this impact and making the necessary amends in our practice of medicine is as important as our diagnostic and technical skills.

(Andavolu MVS. Focus on the Medical History. West J Med 1998; 169:58)

From the Department of Medical Oncology, Los Angeles County–University of Southern California Medical Center, Los Angeles, California.
Reprint requests to Murthy VS Andavolu, MD, 612 West Duarte Rd, Ste 304, Arcadia, CA 91007.

Medicine + Psychiatry™

The Official Journal of the Association of Medicine and Psychiatry

PHYSICIANS INTEGRATING MEDICAL AND PSYCHIATRIC KNOWLEDGE

- Peer-reviewed, quarterly journal of the AMP
- Content originating from the psychiatric problems that present in the primary care setting, emergency room, medical/psychiatric unit, geriatric unit, and consultation service
- Original articles, reviews and case reports
- Clinical case conferences from Mass General Hospital

Charter Rates 4-Issues

❑ $100 Individual ❑ $200 Institutional
❑ $75 In-Training ❑ $250 Outside North America

CALL, FAX, OR WRITE TO SUBSCRIBE:

Phone (804) 817-2000 Fax (804) 817-2020

Medicine + Psychiatry
ARDEN JENNINGS PUBLISHING CO., LTD.
1224 West Main Street, Suite 200
Charlottesville, VA 22903-2858
Payment by check, MasterCard or Visa accepted

ne Western urnal of Medicine On-Line

Your Internet resource for...

www.wjmed.com

CHANGING YOUR ADDRESS?

If you are moving and/or would like your Journal sent to a new address...

1. Print your old mailing address below or attach an old mailing label below:

Name _____
Old Address _____
City _____
State _____
Zip _____
Telephone _____

2. Print or type your new mailing address:

Name _____
New Address _____
City _____
State _____
Zip _____
Telephone _____
Fax _____
E-Mail _____

3. Clip and mail this form to:

The Western Journal of Medicine
1224 West Main Street, Suite 200
Charlottesville, VA 22903-2858

4. Or, visit our web-site at:

http://www.wjmed.com

Western Journal of Medicine

INSTRUCTIONS FOR AUTHORS

In accordance with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (URM), 1997

Our readers represent all branches of medicine. We wish to receive and publish manuscripts that are reliable and lively and that will improve the care of patients, the health of the public, or policies affecting either. Manuscripts should be of interest to a broad range of scholars, busy practitioners, students, and physicians in training who have a clinical orientation. The purpose of a paper or letter may be to report, inform, alert, review, and discuss, but, above all, to teach. Titles should be short and intriguing. Avoid the overuse of jargon, adverbs, and expendable words and phrases; use only standard abbreviations and acronyms; and use inclusive language (see AMA Manual of Style, 8th Edition). We appreciate your interest in The Western Journal of Medicine and our profession.

Manuscript Information

Manuscripts should be sent to the Editor, Linda Hawes Clever, MD, c/o Publisher, The Western Journal of Medicine, 1224 West Main Street, Suite 200, Charlottesville, VA 22903-2858. Manuscripts must be original, not previously published, and not under consideration by another publisher. If preliminary data were included in another presentation or publication, this should be noted in the cover letter, and a copy of that publication should be included. Any conflict of interest, actual or potential, should be revealed to the Editors (see Letter of Transmittal). Obtaining informed consent to protect patients' rights to privacy should be documented according to URM 1997.

All manuscripts should be double-spaced and, including references and abstract but not tables, should not exceed:

- Articles: 3,000 words (15 double-spaced pages)
- Conferences and Reviews: 3,000 words
- Topics in Primary Care Medicine: 3,000 words
- Case Reports, Alerts, and Notices: 1,500 words
- Commentaries: 2,000 words
- Lessons From the Practice: 1,000 words
- Letters to the Editor: 500 words
- Epitomes: 800 words

Manuscripts, except for Case Reports, Epitomes, and Lessons From the Practice, should include a nonstructured abstract of no more than 150–200 words summarizing the article. Abstracts should include a description of the purpose, design, patients, results, and conclusions.

Letters to the Editor must be double-spaced and will be published at the discretion of the Editors. They may be edited for style and brevity. Those of a scientific nature may be subject to peer review. They should be no more than 500 words in length. Authors will be sent page proofs before publication.

All manuscripts will be subject to peer review in addition to review by the Editors to determine the originality, validity, and importance of content and conclusions. Reviewers' comments will be returned with rejected manuscripts at the discretion of the Editors. All reviewers will remain anonymous but will be required to state possible conflicts of interest.

All accepted manuscripts are subject to copyediting, and the corresponding author is sent edited page proofs for approval and necessary minor changes. Excessive changes at this stage may result in a delay of publication or withdrawal of the paper. No changes will be made after the final, edited version has been approved by the corresponding author without notifying the author. It is the corresponding author's responsibility to clear all corrections and changes with coauthors.

Letter of Transmittal

All authors must sign the letter of transmittal, with one author designated as correspondent and his or her name, address, and telephone and fax numbers included.

The order of authorship is determined by the authors. All authors should meet the basic criteria for authorship (as stated below). Because the order of authorship is assigned in different ways, its meaning cannot be inferred accurately unless it is stated by the authors. Authors may explain the order of authorship in a footnote.

A letter of transmittal, except for one accompanying a manuscript from US Government employees whose work was done as part of their official duties, must include a paragraph that transfers copyright: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns, or otherwise conveys all copyright ownership to The Western Journal of Medicine, in the event that such work is published by the journal."

The letter of transmittal must include a statement of author responsibility signed by all authors: "I have participated in the conception and design of this work and in the writing of the manuscript and take public responsibility for it. I have reviewed the final version of the manuscript and approve it for publication. I attest to the validity and legitimacy of data in the manuscript and agree to be named as the lead author or coauthor of the manuscript."

The letter of transmittal must include a description of sources of funding and the role of sponsors, including their involvement, if any, in review and approval of the manuscript for publication. The letter must also include a statement of financial disclosure: "I warrant that I have no financial interest in the drugs, devices, or procedures described in the enclosed manuscript (except as disclosed in the attached statement)."

Research or project support should be included as a footnote to the manuscript or in the accompanying cover letter.

Manuscripts concerned with experimental investigation on human subjects must include in the text a statement that all subjects gave their informed consent and that approval was obtained from the appropriate ethics committee.

Acknowledgments will be printed on a select basis—to acknowledge those who contributed to but were not involved in the writing or review of the paper. They should not include persons whose work on the manuscript was a part of their regular duties.

Preparation of Manuscripts

Everything, including references, tables, figure legends, and abstracts, must be double-spaced.

Please submit the following: The original manuscript, two copies, and a copy of the manuscript on disk (labeled with the word processing program used). Allow a margin of 2.5 to 4 cm (1 to 1.5 in) on both sides. Be sure to include the references, tables, and figure legends on the disk. Formatting should be kept to a minimum. Manuscripts transmitted by facsimile machine are not acceptable unless requested by the Editors.

All values should be in Systeme International (SI) units, with metric equivalents following in parentheses. Tempera-ture readings should be given in Celsius. Use the generic name of drugs, with the salt or ester given at the initial mention of a drug.

Figures (illustrations) should be submitted in triplicate in black and white, unmounted 12.7 X 17.8 cm (5 X 7 in) glossy prints, with the figure number, lead author's name, and top of the photo indicated with a label on the back. Patients (and relatives) have a right to anonymity in published clinical documentation. Details that might identify patients should be avoided unless essential for scientific purposes. Masking of the eye region in photographs of patients may be inadequate protection of anonymity. If identification of patients is unavoidable, informed consent should be obtained. This should be clearly stated and proof submitted with the manuscript. Changing the data on patients should not be used as a way of securing anonymity.

Figure legends, to be typed in sequence on the same page, should be in complete sentences. Any figures or tables previously published must be accompanied by a letter of permission to borrow from the copyright holder (the previous publisher). The permission of the authors should also be obtained. The Editors discourage the use of borrowed figures or tables.

Reprints

A form for ordering reprints will be sent to the corresponding author when the article is published.

References

All references should be cited in the text using superscript numbers and listed in their order of citation. They should be pertinent to the text and not simply a listing of the results of a computerized search. They should be in URM style according to the following examples. Do not use op cit or ibid.

References should be medical, scientific, or scholarly publications. Others—such as newspapers or magazines—should be kept to a minimum.

Journal Articles

Abbreviations of journal titles should conform to those used in Index Medicus. List up to six authors; for seven or more, use et al after listing the first six.

1. Vega KJ, Pina I, Krevsky B. Heart transplantation is associated with an increased risk for pancreatobiliary disease. Ann Intern Med 1996; 124:980–983
2. Parkin DM, Clayton D, Black RJ, Masuyer E, Friedl HP, Ivanov E, et al. Childhood leukaemia in Europe after Chernobyl: 5 year follow-up. Br J Cancer 1996; 73:1006–1012

No author given:

3. Cancer in South Africa [editorial]. S Afr Med J 1994; 84(12):15

Books

4. Ringsven MK, Bond D. Gerontology and leadership skills for nurses. 2nd ed. Albany (NY): Delmar Publishers; 1996 [author of book is same as author of chapter]
5. Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press; 1995, pp 465–478 [authors of book differ from chapter author]

Correspondence

6. Shusterman D. Espresso maker's wrist [correspondence]. West J Med 1990; 152:721–722

Scientific or Technical Report

Issued by funding or sponsoring agency:

7. Smith P, Golladay K. Payment for durable medical equipment billed during skilled nursing facility stays. Final report. Dallas (TX): Dept of Health and Human Services (US), Office of Evaluation and Inspections; 1994 Oct. Report No.: HHSIGOEI69200860

Issued by performing agency:

8. Field MJ, Tranquada RE, Feasley JC, editors. Health services research: work force and educational issues. Washington DC: National Academy Press; 1995. Contract No.: AHCPR282942008. Sponsored by the Agency for Health Care Policy and Research
9. Centers for Disease Control and Prevention. Recommendations and Reports: 1997 Revised guidelines for performing CD4+ T-cell determinations in persons infected with human immunodeficiency virus (HIV) MMWR 1997; 46(Jan 10):RR-2

Proceedings

10. Kimura J, Shibasaki H, editors. Recent advances in clinical neurophysiology. Proceedings of the 10th

International Congress of EMG and Clinical Neurophysiology; 1995 Oct 15–19; Kyoto, Japan. Amsterdam: Elsevier; 1996

Mass Circulation Publications

11. Lee G. Hospitalizations tied to ozone pollution: study estimates 50,000 admissions annually. The Washington Post 1996 Jun 21; Sect A:3 (col 5)

Personal Communications and Unpublished Data

The use of "personal communication" or "unpublished data" should be avoided and should not be included in the reference list. If such a notation provides essential information not available from a public source, it should be given in parentheses in the body of the text, listing the person's name, highest academic degrees, and professional affiliation, whether the communication was oral or written, and the date (month and year):
12. Lyme disease has been reported in red squirrels (J. Sneed, PhD, Department of Wildlife, written communication, September 1990).

For Further Information

Questions regarding the Instructions for Authors may be directed to the Managing Editor, Allison Spearman, 1224 W. Main St., Ste. 200, Charlottesville, VA 22903-2858. Telephone (804) 979-8034, Fax (804) 979-4025.

Additional copies of Instructions for Authors are also available through an on-demand fax request line 24 hours a day. Call (804) 979-8034 to receive a faxed copy of the Instructions for Authors.

AUTHOR CHECKLIST

- ✓ Original manuscript and 2 copies; diskette.
- ✓ Everything double-spaced.
- ✓ Illustrations, black and white glossy, identified with lead author's name—3 sets, plus figure legends that describe fully and in complete sentences what the figure depicts.
- ✓ Letter of transmittal that includes release of copyright, statement of conflict of interest, funding source(s), and authorship responsibility, signed by all the authors.
- ✓ A 200-word unstructured abstract.
- ✓ Title page that includes current affiliation of all authors and an address and telephone and fax number for corresponding author.
- ✓ Permission-to-borrow letters for any previously published illustrations or tables.
- ✓ All references numbered consecutively, double-spaced, in URM style, and cited in text. No unpublished data or nonscientific publications listed in references (include in text).
- ✓ Informed consent obtained.

Classified Advertisements

The rate for each insertion is **$1.50 per word, with a 30 word ($45) minimum.** Confidential box number charge: $10 each month.
A word is defined as one or more letters bounded by spaces. The following gives some examples:

Linda H. Clever, MD = 4 words	
Send CV	= 2 words
A	= 1 word
February 22, 1997	= 3 words
allergy/immunology	= 1 word
Sacramento, CA 95817	= 3 words
804-979-8034	= 1 word

Classified display rate $70 per inch. Maximum sizes: 1 column by 5" or 2 columns by 2" (2-1/8" per column). Larger classified ad space by special arrangements.
Copy for classified advertisements should be received not later than **first of the month preceding issue. All copy must be typed or printed.** Classified advertisers using Box Numbers forbid the disclosure of their identity; your inquiries in writing will be forwarded to Box Number advertisers. Although *The Western Journal of Medicine* believes the classified advertisements in these columns to be from reputable sources, we do not investigate the offers made and assume no liability concerning them. The right is reserved to reject, withdraw, or modify all classified advertising copy in conformity with the decisions of the Advertising Committee.

Please Type or Print Advertising Copy

Classified Advertisements Are Payable in Advance
CLASSIFIED ADVERTISEMENTS, THE WESTERN JOURNAL OF MEDICINE
2 WEST TAUNTON AVENUE, BERLIN, NJ 08009
(609) 768-9360; FAX (609) 753-0064
Ads may be placed online at www.wjmed.com

PHYSICIANS WANTED

OREGON AND THE NORTHWEST. Urban, suburban, rural locations; variety of practice arrangements; all specialties. Placement professionals for 20 yrs. Oberto & Associates, 920 Pinecrest Terr, Ashland, OR 97520. (800) 482-6656; FAX (541) 482-4951. No J-1 Opp. boberto@jeffnet.org.

Medical Research Associate - needed to plan and conduct scientific and medical research concerning medical and related aspects of the energy systems of the human body. The position requires a M.S. in health sciences or related field and 2 years experience as a medical laboratory researcher. Also required: Demonstrable , in depth knowledge of: 1) human neurological systems. 2). human anatomy, physiology, physics and biophysics of brain and neurological system 4) scientific medical research techniques, including mathematical modeling, statistical analysis, data compilation into technical research publications. The position is full-time 40 hours per week and pays $29,003/yr. Applicants to send resumes to Department of Workforce Services, Atten: Pat Redingtion, Job Order #3060587, 140 East 300 South - 1st Floor, SLC, UT 8411.

GASTROENTEROLOGY/HEPATOLOGY - The Division of Gastroenterology and the Department of Internal Medicine, at the University of California, Davis, School of Medicine is recruiting a full-time transplant hepatologist at the Assistant/Associate Professor level. Candidates must possess an M.D. degree; be Board certified/eligible in Internal Medicine and Gastroenterology with subspecialty training in transplant hepatology. Individual must be eligible as a UNOS approved transplant physician as well as be eligible for licensure in the State of California. Duties will include: patient care in in-patient and out-patient clinical settings, clinical or basic science research, and teaching of residents and fellows. The candidate will have direct responsibilities as an integral member of the liver transplant team and will hold an academic appointment in the Division of Gastroenterology. Please forward curriculum vitae to: Timothy Albertson, M.D., Ph.D., c/o Renee Korte, Department of Internal Medicine, University of California, Davis, P.O. Box 179002, Sacramento, CA 95817-9002. This position is open until filled but no later than December 31, 1998. The University of California, Davis, is an Affirmative Action/Equal Opportunity Employer.

MEDICAL NEWSLETTERS

HOW TO PASS BOARD OF INTERNAL MEDICINE

For first FREE issue (24 pages)
Send $5 to cover post & hand to:

ARORA BOARD REVIEW

389 East Mt. Pleasant Avenue
Livingston, NJ 07039

PHYSICIANS WANTED

IDAHO

Make One Of America's Best Places to Live Even Better.

Where You'll Work.
Primary Health, Idaho's largest, fastest-growing integrated health care system whose network of family medicine immediate care centers, by-appointment family practitioners, pediatricians and OB/GYNs serves beautiful southern Idaho.

Where You'll Live.
In a great place to raise a family with quality schools, incredible outdoor recreation and a rural atmosphere close to a metropolitan area with a beautiful performing arts center, excellent hospitals and professional sports.

What You'll Get.
The financial backing and medical resources of a major health care network. A competitive salary, ownership options, flexible work and call schedules, professional growth, full benefits including medical and dental and much more.

Submit CV and questions to:
BECKY NELSON
(800) 688-5008 ext. 507 • FAX (208) 344-4262
Physician Recruitment
800 Park Boulevard, Suite 760
Boise, Idaho 83712

Primary Health

CALIFORNIA

Int-rim PHYSICIANS

LOCUM TENENS
PERMANENT PLACEMENTS

Jim Ellis (800) 437-7676

PHYSICIANS WANTED

FAMILY PRACTICE

OREGON/SOUTHWEST WASHINGTON

Northwest Permanente, P.C., a stable, physician-managed multispecialty group of over 550 physicians providing quality care to 430,000 members of Kaiser Permanente in Oregon and Southwest Washington, has excellent opportunities for board certified or eligible family physicians. Our medical offices in Portland, Oregon have an outpatient clinical position that includes some urgent care; and our group in Longview has one position that requires OB skills and a second position that is primarily urgent care.

Our program offers a professionally stimulating practice in one of the most successful managed care systems in the country. We also offer a competitive salary (signing bonus for Longview), and a full benefits package including a generous retirement program, professional liability coverage, sabbatical leave and more. To receive additional information, please forward inquiry and CV to: W.J. Clark, Director of Professional Resources, Northwest Permanente, P.C., 500 NE Multnomah, Suite 100, Portland, OR 97232-2099. (800) 813-3763. EOE.

KAISER PERMANENTE
Northwest Permanente, P.C.
Physicians and Surgeons

PHYSICIANS WANTED

OCCUPATIONAL MEDICINE Locum Tenens Pacific Northwest - Northwest Permanente, P.C., a physician-managed, multispecialty group, has a full-time, six-month to one-year locum tenens opportunity available for a Board Certified and/or residency trained occupational medicine physician or other relevant primary care trained physician, at our medical offices in Oregon and Southwest Washington. Our Occupational Health Program has 19 physicians and covers outpatient clinics at nine sites with 65,000 visits per year, an Employee Health Service, and an Environmental Safety Program serving nearly 6,000 employees. We offer a competitive salary and benefit package which includes family medical insurance, paid time off, professional liability coverage, and a relocation allowance. Please forward C.V. to: W.J. Clark, Director of Professional Resources, NORTHWEST PERMANENTE, P.C., 500 NE Multnomah St., Suite 100, Portland, OR 97232-2099. (800) 813-3763. EOE.

General Physicians and Internists: Salary range from $77,256 to $103,884. Western State Hospital is a fully accredited (JCAHO) and certified (HCFA) 1002 bed hospital serving adult, geriatric and forensic populations. The hospital is associated with the University of Washington. Western currently has a physicians' staff of 54, including 36 psychiatrists and 13 other nonpsychiatric physicians. Excellent benefits, including hospitalization/medical insurance, retirement, vacation estimated equivalence at 30%, plus optional deferred income plan. Send CV to Jerry Dennis, MD; CEO; Western State Hospital; 9601 Steilacoom Blvd. SW; Tacoma, WA 98498-7213

PHYSICIANS WANTED

A Practice Opportunity in Western Washington - on the coast, in a city of 50,000 people, 90 miles from Seattle and 50 miles from Vancouver, B.C. Busy Pulmonologist seeks Board Certified INTERNIST who is intense and comfortable with all aspects of ICU work. Delightful place to practice in a small university town. Responses to: William E. Waltner, M.D. 2950 Squalicum Parkway, Bellingham, WA 98225 (360) 733-1405, (360) 733-9449

Since 1979
the

LOCUM TENENS NETWORK has been taking the hassles of the paperwork and overhead out of practicing medicine. Practice near home or travel the country. We will coordinate all your travel details and provide you with the best occurrence malpractice policy available. Explore a partnership with Interim Physicians and open new horizons for your future.

Call today! (800) 333-7828

WESTERN STATES OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 100 positions of various specialties. Both permanent and locum tenens. Send CV to:

Western States Physician Services
7510 No. Trellis Circle, Fresno, CA 93720
Call (800) 873-0786; FAX (800) 705-7943
email: weserve@lightspeed.net

PHYSICIANS WANTED

OCCUPATIONAL MEDICINE

Portland, Oregon

Northwest Permanente, P.C., a physician-managed multispecialty group, has a full-time opportunity available for a Board Certified and/or residency trained occupational medicine physician, or other relevant primary care trained physician, at our medical offices in Portland, Oregon. Our new associate will need a background in minor injury care with a base knowledge of exposures, as well as the ability to participate in case management.

Kaiser Permanente's Occupational Health Program in the Northwest Region (Oregon/Washington) has a total of 19 physicians and covers outpatient clinics at nine sites with 65,000 visits per year, an Employee Health Service, and an Environmental Safety Program serving nearly 6,000 employees. There are plans to expand our services in the area of national occupational medicine consulting.

We offer a competitive salary and benefits package which includes two comprehensive pension plans, paid professional liability, sabbatical leave and more. Please forward CV to: W.J. Clark, Director of Professional Resources, NORTHWEST PERMANENTE, P.C., 500 NE Multnomah, Suite 100, Portland OR 97232-2099. EOE

KAISER PERMANENTE
Northwest Permanente, P.C.
Physicians and Surgeons

REPRINTS

Any article printed in *The Western Journal of Medicine* can be purchased in quantities of 100 or more. Printed on quality journal stock.

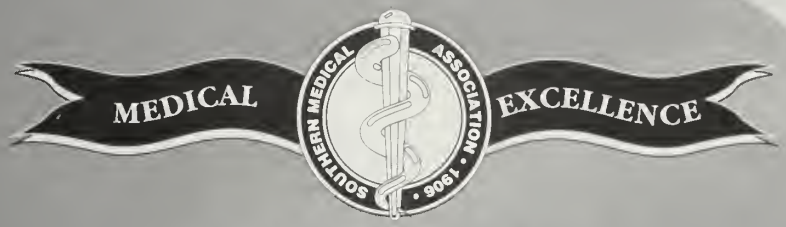
Prices are based upon article length and quantity ordered

For information, call:
Susan Robinson
(804) 817-2010, ext.118;
Fax (804) 817-2020
or E-Mail to:
srobinson@cjp.com

ADVERTISING INDEX

THE QUEST FOR MERCY . . . . . .2nd Cover
Southern Medical Association . . .3rd Cover
MEDICINE + PSYCHIATRY . . . . . .4th Cover

Your CME Resource



SOUTHERN MEDICAL ASSOCIATION

The Inaugural Conference on

DIABETES

Advances in Management and Prevention

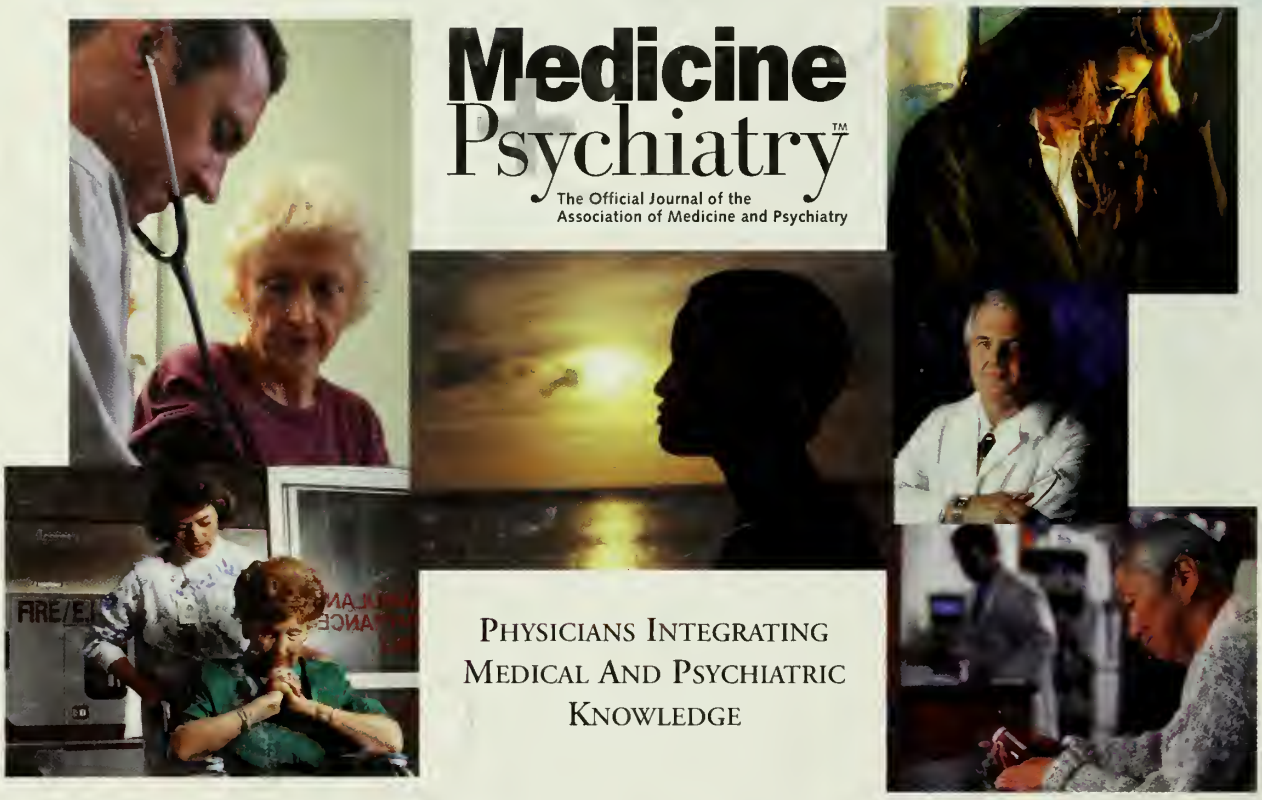
September 25-27, 1998
Pinehurst Resort and Country Club
Pinehurst, North Carolina

For more information or to register,
call 800-433-4992.

The Southern Medical Association is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

SMA- The Leading Provider of CME in the South

Charter Subscription Rate!



- Original articles, reviews and case reports
- Clinical case conferences from Massachusetts General Hospital
- Content originating from the psychiatric problems that present in the primary care setting, emergency room, medical/psychiatric unit, geriatric unit, and consultation service

Charge my: ❑ Visa ❑ MasterCard ❑ Check enclosed ❑ Bill me

Card # _____

Exp. Date _____

Signature _____

Name _____

Institution/Title _____

Medical Specialty _____

Percentage of professional time spent: ___%Clinical ___%Research

___%Teaching ___%Admin. ___%Other _____

Address _____

City, State, Zip _____

Phone _____

Fax _____

Check One (4 issues)

- ❑ $100 Individual Charter Rate
- ❑ $200 Institutional Rate
- ❑ $75 In-Training Rate
- ❑ $250 Outside North America

SMJ98

Return to: Medicine + Psychiatry, 1224 West Main Street, Suite 200
Charlottesville, VA 22903-2858 Phone (804) 979-4913 Fax (804) 979-4025

OFFICIAL JOURNAL OF

ARIZONA MEDICAL ASSOCIATION · CALIFORNIA MEDICAL ASSOCIATION · DENVER MEDICAL SOCIETY · IDAHO MEDICAL ASSOCIATION · NEVADA STATE MEDICAL ASSOCIATION · NEW MEXICO MEDICAL SOCIETY · UTAH MEDICAL ASSOCIATION · WASHINGTON STATE MEDICAL ASSOCIATION · WYOMING MEDICAL SOCIETY

The Western Journal of Medicine

VOLUME 169 • NUMBER 2

AUGUST 1998

ARTICLES

74 Insight on Emphysema—The First 300 Cases of Surgical Treatment
R J FISCHEL, R J MCKENNA, JR, A GELB, N SINGH, and M BRENNER

78 Splenomegaly in 2,505 Patients at a Large University Medical Center From 1913 to 1995—1913 to 1962: 2,056 Patients
R A O'REILLY

88 Splenomegaly in 2,505 Patients at a Large University Medical Center From 1913 to 1995—1963 to 1995: 449 Patients
R A O'REILLY

98 Insulinoma—Experience from 1950–1995
M P BOUKHMAN, J H KARAM, J SHAVER, A E SIPERSTEIN, Q-Y DUH, and O H CLARK

105 Fundamentals—Rudolf Virchow and Modern Medicine
D M REESE

EPITOMES

109 Important Advances in Clinical Medicine

ALERTS, NOTICES, AND CASE REPORTS

114 Chronic Lymphocytic Leukemia in a Patient With Sickle Cell Anemia
H S KIM, L YOSPUR, and Y NIIHARA

116 Suppurative Parotitis
D C SHEPPARD and H F CHAMBERS

COMMENTARY

118 Society and Public Health—Crisis and Rebirth
J M MANN

OTHER FEATURES

68 Continuing Medical Education Activities

122 Instructions for Authors

125 Classified Advertising

127 Subscription Information

Detailed Table of Contents: 66, 67

DISPLAY SHELVES

Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Medical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology

THE FRANCIS A. COUNTWAY
LIBRARY OF MEDICINE
BOSTON, MA

AUG 19 1998

MEDICAL EXCELLENCE

SMA – Your CME Resource

Southern Medical Association 92nd Annual Scientific Assembly

November 18-22, 1998
New Orleans, Louisiana
Ernest N. Morial Convention Center

Guest Speakers

These speakers were confirmed at press time. More will be confirmed later.

Allergy & Immunology
Ernest N. Charlesworth, M.D., Brenham, Tex.
I. Celine Hanson, M.D., Houston, Tex.

Cardiology
Bruce Lindsay, M.D., St. Louis, Mo.

Colon & Rectal Surgery
John Pemberton, M.D., Rochester, Minn.
George Fuhrman, M.D., New Orleans, La.

Dermatology
Vincent A. DeLeo, M.D., New York, N.Y.
Stephen E. Wolverton, M.D., Indianapolis, Ind.

Emergency Medicine
Larry Mellick, M.D., Augusta, Ga.
Rick Dart, M.D., Denver, Colo.

Family Practice
Martin Sullivan, M.D., Durham, N.C.
Frank Svec, M.D., Ph.D., New Orleans, La.

Gastroenterology
Charles Sninsky, M.D., Gainesville, Fla.
Eugene R. Schiff, M.D., Miami, Fla.

Geriatric Medicine
Charles A. Cefalu, M.D., New Orleans, La.
Laura Chiodo, M.D., San Antonio, Tex.

Gynecology
G. Rodney Meeks, M.D., Jackson, Miss.

Medical Management & Administration
Robert L. Marier, M.D., New Orleans, La.
Jane M. Orient, M.D., Tucson, Ariz.

Medicine
Dick Briggs, Jr., M.D., Birmingham, Ala.
Blase Carabello, M.D., Charleston, S.C.

Neurology & Psychiatry
Christopher C. Colenda, M.D., East Lansing, Mich.
Salvador Ceniceros, M.D., Johnson City, Tenn.

Neurosurgery
Peter J. Jannetta, M.D., Pittsburgh, Penn.
John D. Jackson, M.D., New Orleans, La.

Occupational & Environmental Medicine
Edward J. Doyle, Jr., M.D., M.S.C., Morgantown, W. Va.
John Walden, M.D., Huntington, W. Va.

Oncology
Kent Wallner, M.D., Seattle, Wash.
Susan Miesfeldt, M.D., Charlottesville, Va.

Ophthalmology
Kurt A. Buzard, M.D., F.A.C.S., Las Vegas, Nev.

Orthopaedic & Trauma Surgery
Gerald Engh, M.D., Arlington, Va.

Otolaryngology - Head & Neck Surgery
C. Blake Simpson, M.D., San Antonio, Tex.
Thomas B. Aufdemorte, D.D.S., San Antonio, Tex.

Pathology
John W. Bishop, M.D., Omaha, Neb.
Charles B. Root, M.D., West Dundee, Ill.

Pediatrics & Adolescent Medicine
Russell W. Steele, M.D., New Orleans, La.
Franklin G. Boineau III, M.D., New Orleans, La.

Plastic & Reconstructive Surgery
James Grotting, M.D., F.A.C.S., Birmingham, Ala.
John J. Coleman III, M.D., Indianapolis, Ind.

Radiology
Christopher R. B. Merritt, M.D., New Orleans, La.
Eva Rubin, M.D. Birmingham, Ala.

Rheumatology
Fred Wolfe, M.D., Wichita, Kan.
Virginia Steen, M.D., Washington, D.C.

Surgery
Edward L. Bradley III, M.D., Buffalo, N.Y.
J. David Richardson, M.D., Louisville, Ky.

Urology
Jonathan P. Jarow, M.D., Baltimore, Md.

CME Opportunities

- Twenty-eight Specialty Section meetings and a number of joint meetings
- Scientific and Clinical Symposia - "early bird" symposia with free breakfast and mid-day symposia with free lunch
- Case-driven Grand Rounds - Controversial Diagnoses 1998: Prostate Cancer; Domestic Violence; Incontinence; Neck Pain; Occupational Medicine and the Primary Care Physician
- "Dessert with the Experts" with Specialty Section guest speakers
- Special 2-hour "New Drugs Update" Symposium - part of SMA's Section Officers' Recognition Luncheon
- Managed Care Track on important nonclinical issues - contracting, capitation, forming physician organizations, improving practice efficiency, reimbursement and compliance
- Women's Health Track to focus on issues in women's health
- The President's Symposium - "Physician Leadership for the Next Century"

Special Events

Enhance your CME experiences with special events.

Opening Ceremony
Thursday, November 19, 8:30 - 10:00 AM
The keynote address by SMA President J. Lorin Mason, M.D., marks the official start of the 92nd Annual Scientific Assembly. Entertainment and introduction of other SMA leaders will round out the program. This program is free to registered participants.

Section Social Functions, New Member Reception, and Alumni Reunions
Thursday, November 19, times vary

Prayer Breakfast
Friday, November 20, 7:00 - 8:00 AM
Initiated last year, this popular event offers an environment of fellowship and worship. This program is free to registered participants.

President's Reception
Friday, November 20, 7:30 PM
Let the good times roll at the annual President's Reception, featuring a masked ball (costume optional) at Mardi Gras World. Tickets are $35/Adult and $15/Child 12 or younger.

President's-Doctor's Day Awards Luncheon
Saturday, November 21, 12:30 - 2:30 PM
Nationally known columnist and entertaining food critic Calvin Trillin will be the featured speaker. Tickets are $30 each.

President's Night Dinner Dance
Saturday, November 21, 6:30 - 11:30 PM
Great food and the heritage of Southern music will highlight the President's Night Dinner Dance. And the Pink Flamingos are back to add their special brand of entertainment. Tickets are $85/Adult and $35/Child 12 or younger.

For more information, call 800-423-4992

And more!!

- Insurance & Retirement Programs
- Exhibit Hall Activities
- Recreational Activities (Golf & Tennis Tournaments, Fun Run/Walk)
- Enrichment Programs
- Programs for Active Retired Members
- Over 30 hours of CME Credit offered for only $195.00 for SMA Members, $295 for Joining Members, and $445 for Nonmembers, and free for Medical Student, Residents and Fellows

The Southern Medical Association is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

92nd Annual Scientific Assem

November 18-22 • New Orleans, Louisi

The Western Journal of Medicine®

SINCE 1902

CARDEN JENNINGS PUBLISHING COMPANY LTD

A PUBLICATION OF CARDEN JENNINGS PUBLISHING CO, LTD • 1224 WEST MAIN STREET, SUITE 200 • CHARLOTTESVILLE, VIRGINIA 22903-2858
TELEPHONE (804) 817-2000; FACSIMILE (804) 817-2020; E.MAIL wjm@cjp.com

LINDA HAWES CLEVER, MD, *Editor*
EDWARD D HARRIS JR, MD, *Associate Editor*
WILLIAM T CARDEN JR, *Publisher*

ALLISON SPEARMAN, *Managing Editor*
DAVID ERN, *Marketing Director*

SARAH BRUCE, *Senior Copy Editor*

editorial communications to DR CLEVER • business communications to MS SPEARMAN

Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Medical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

SPECIAL EDITORS

Special Editor for Arizona
Marshall B. Block, Phoenix, Ariz

Special Editor for Denver
David Shander, Denver, Colo

Special Editor for Idaho
E. R. W. Fox, Coeur d'Alene, Idaho

Special Editor for Nevada
Anton P. Sohn, Reno, Nev

Special Editor for New Mexico
I. Brian Taylor, Carlsbad, NM

Special Editor for Utah
C. Basil Williams, Salt Lake City, Utah

Special Editor for Washington
David Hopkins, Federal Way, Wash

Special Editor for Wyoming
Joseph P. Murphy, Casper, Wyo

ASSISTANT EDITORS

Clinical Investigation
H. Benfer Kaltreider

Health and Public Policy
Ralph Crawshaw

International Health
Anvar Velji

Lessons From the Practice
Stephen J. McPhee
Jonathan E. Rodnick

Medical Staff Conferences
Nathan M. Bass

Poetry
Margaret Kaufman

Primary Care Medicine
Stephen J. McPhee
Terrie Mendelson

Radiologic Cases
Jonathan M. Levy

EDITORIAL BOARD

Editor Emeritus
Malcolm S. M. Watts, San Francisco, Calif

Anesthesiology
Carol Lake, Sacramento, Calif

Biostatistics and Epidemiology
Virginia L. Ernster, San Francisco, Calif

Cardiac and Thoracic Surgery
Norman E. Shumway, Stanford, Calif

Dermatology
Clifton R. White Jr, Portland, Ore

Emergency Medicine
William A. Boehm, Alamogordo, NM

General and Family Practice
Norman Kahn, Kansas City, Mo
Thomas E. Norris, Seattle, Wash
Joe Schoeber, Casper, Wyo

Internal Medicine
Albert Deisseroth, Houston, Texas
Alan Fogleman, Los Angelas, Calif
Patricia Gabow, Denver, Colo
John H. Holbrook, Salt Lake City, Utah
Philip Hopewell, San Francisco, Calif
Irwin J. Schatz, Honolulu, Hawaii
Walter E. Stamm, Seattle, Wash
Reginald Strickland, Albuquerque, NM
Stephen I. Wasserman, San Diego, Calif

Neurology
Robert Collins, Los Angeles, Calif
John Greenlee, Salt Lake City, Utah
Leslie Wiener, Los Angeles, Calif
Earl Zimmerman, Portland, Ore

Neurosurgery
George A. Ojemann, Seattle, Wash
Robert F. Spetzler, Phoenix, Ariz

Nuclear Medicine
Jerold M. Lowenstein, San Francisco, Calif

Obstetrics and Gynecology
Daniel Mishell Jr, Los Angeles, Calif

Occupational Medicine
Linda Rosenstock, Washington, DC

Ophthalmology
Sandy Feldman, La Jolla, Calif

Orthopedics
Thomas DeCoster, Albuquerque, NM

Pathology
Ronald Weinstein, Tuczon, Ariz

Pediatrics
Allen W. Mathies Jr, Pasadena, Calif
Diane Wara, San Francisco, Calif

Pharmacology
Rubin Bressler, Tucson, Ariz

Physical Medicine and Rehabilitation
Julie G. Madorsky, Pomona, Calif

Preventive Medicine and Public Health
Joseph L. Lyon, Salt Lake City, Utah

Psychiatry
J. Christian Gillin, San Diego, Calif
Lewis Judd, La Jolla, Calif

Radiology
Gary Glazer, Stanford, Calif
Michael L. Manco-Johnson, Denver, Colo
Albert A. Moss, Seattle, Wash

Surgery
Haile T. Debas, San Francisco, Calif
Alex G. Little, Las Vegas, Nev

Urology
Linda Shortliffe, Stanford, Calif

Senior Members at Large
Thomas Elmendorf, Davis, Calif
Edgar Wayburn, San Francisco, Calif

ADVISORY BOARD, CLINICAL INVESTIGATION

Brian A. Cason, San Francisco, Calif
John Christenson, Salt Lake City, Utah
Kari Connolly, San Francisco, Calif
Bruce W. Goldberg, Portland, Ore
Philip Goodman, Reno, Nev
Roy Jones, Albuquerque, NM
Howard Lien, Tucson, Ariz
Barbara M. Lippe, Los Angeles, Calif
Michael W. McDermott, San Francisco, Calif
Jeanette Mladenovic, Denver, Colo
Kenneth M. Moser, San Diego, Calif
James C. Orcutt, Seattle, Wash
John Owings, Sacramento, Calif
Robert Robbins, Stanford, Calif
Henry Rosen, Seattle, Wash
Mary H. Samuels, Portland, Ore
George A. Sarosi, San Jose, Calif
Jeffrey Saver, Los Angeles, Calif
David Schriger, Los Angeles, Calif
Jack H. Simon, Denver, Colo
Peggy Sue Weintrub, San Francisco, Calif
Owen M. Wolkowitz, San Francisco, Calif

DISPLAY & CLASSIFIED ADVERTISING INFORMATION

CONTACT: MJ Mrvica Associates, Inc, 2 West Taunton Ave, Berlin, NJ 08009 • (609) 768-9360/FAX (609) 753-0064

Advertisements—The journal is published the second week of the month. Display advertising must be received no later than the first of the month preceding issue. Advertising rates will be sent on request. Acceptance of advertising is contingent upon approval by the Publisher.

The journal reserves the right to reject any advertisement.

SUBSCRIPTION INFORMATION

The subscription price per year is $65 in the United States and Canada (US funds); $80 in all other countries. Institutional rate $90. Single copies are $10. Special issues are $10. Address all subscription communications to:

THE WESTERN JOURNAL OF MEDICINE Circulation, 1224 W Main St, Suite 200, Charlottesville, VA 22903-2858 • Tel: (804) 817-2000

Allow six weeks for subscriptions to begin. Past issues must be bought individually. So long as reserve stocks are available, missing issue requests from subscribers are honored for up to six months after the issue date. Thereafter, the single copy rate of $10 is applicable for each issue available. Special issues are $10.

Change of Address—Requests for change of address should give both the old and new address. Allow six weeks for changeover.

SUBMITTING MANUSCRIPTS

Manuscripts for consideration should be sent to the managing editor, Allison Spearman, 1224 W Main St, Suite 200, Charlottesville, VA 22903-2858.

"Instructions for Authors"—A complete guide to manuscript submission and *WJM* style available from the publisher. Manuscripts may be prepared in accordance with the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals."

PUBLISHER

Copyright © 1998 by Carden Jennings Publishing Co, Ltd • Owned and Published by Carden Jennings Publishing Co, Ltd

All material subject to this copyright appearing in THE WESTERN JOURNAL OF MEDICINE may be photocopied for the noncommercial purpose of scientific or educational advancement. Volumes begin with January and July.

THE WESTERN JOURNAL OF MEDICINE (ISSN 0093-0415/USPS 084 480) is published monthly by Carden Jennings Publishing Co, Ltd, 1224 W Main St, Charlottesville, VA 22903-2858. Periodicals postage paid at Easton, Pennsylvania.

POSTMASTER: Send address changes to *The Western Journal of Medicine*, Circulation, 1224 W Main St, Suite 200, Charlottesville, VA 22903-2858.

The Western Journal of Medicine

VOLUME 169 • NUMBER 2 • AUGUST 1998

CONTENTS

ARTICLES

74 **Insight on Emphysema—The First 300 Cases of Surgical Treatment**

RICHARD J. FISCHEL, MD, PhD; ROBERT J. MCKENNA, JR, MD; ARTHUR GELB, MD; NARINDAR SINGH, MD; and MATTHEW BRENNER, MD

From the Lung Center, Chapman Medical Center, Orange, California.

78 **Splenomegaly in 2,505 Patients at a Large University Medical Center From 1913 to 1995—1913 to 1962: 2,056 Patients**

ROBERT A. O'REILLY, MD

From the Departments of Medicine, University of California, San Francisco, School of Medicine; Stanford University Medical Center, Palo Alto; and Santa Clara Valley Medical Center, San Jose, California.

88 **Splenomegaly in 2,505 Patients at a Large University Medical Center From 1913 to 1995—1963 to 1995: 449 Patients**

ROBERT A. O'REILLY, MD

From the Departments of Medicine, University of California, San Francisco, School of Medicine; Stanford University Medical Center, Palo Alto; and Santa Clara Valley Medical Center, San Jose, California.

98 **Insulinoma—Experience from 1950 to 1995**

MILANA P. BOUKHMAN; JOHN H. KARAM, MD; JOHN SHAVER, MD; ALLAN E. SIPERSTEIN, MD; QUAN-YANG DUH, MD; and ORLO H. CLARK, MD

From the Department of Surgery, University of California, San Francisco/Mount Zion Medical Center.

105 **Fundamentals—Rudolf Virchow and Modern Medicine**

DAVID M. REESE, MD

From the Division of Hematology-Oncology, University of California, Los Angeles, School of Medicine.

EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

Urology

Items of progress in urology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, as to both scientific fact and important clinical significance.

109 **Best Screening Tests for Prostate Cancer**

JUDD W. MOUL, MD

110 **Urolithiasis**

NOAH S. SCHENKMAN, MD; and MARSHALL L. STOLLER, MD

111 **Epidemiology of Prostate Cancer**

ANANIAS C. DIOKNO, MD

112 **Sildenafil—A Milestone in the Treatment of Impotence**

DANIEL NACHTSHEIM, MD

ALERTS, NOTICES, AND CASE REPORTS

114 **Chronic Lymphocytic Leukemia in a Patient With Sickle Cell Anemia**

HYUN SUE KIM, MD; LISA YOSPUR, MD; and YUTAKA NIIHARA, MD

From the Departments of Medicine and Pathology, Harbor-UCLA Medical Center, UCLA School of Medicine, Torrance, California.

116 **Suppurative Parotitis**

DONALD C. SHEPPARD, MD and HENRY F. CHAMBERS

From the Medical Service, San Francisco General Hospital, Department of Medicine, University of California San Francisco.

COMMENTARY

118 **Society and Public Health—Crisis and Rebirth**

JONATHAN M. MANN, MD, MPH

From the School of Public Health, Allegheny University of the Health Sciences, Philadelphia, PA.

OTHER FEATURES

68 **Continuing Medical Education Activities**

122 **Instructions for Authors**

125 **Classified Advertising**

127 **Subscription Information**

★ Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

THE FRANCIS A. COUNTWAY
LIBRARY OF MEDICINE
BOSTON, MA

AUG 1 9 1983

Continuing Medical Education

ARIZONA • CALIFORNIA, HAWAII, NEVADA • COLORADO • IDAHO • NEW MEXICO • UTAH • WASHINGTON • WYOMING

ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (520) 626-7832; (800) 328-5868.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Paulette Richardson, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-3387. For more information on accreditation or certification, please write to the above address.

ALLERGY/IMMUNOLOGY

August 6–9—**A Midsummer Night's Wheeze.** California Society of Allergy, Asthma, and Immunology at La Costa Resort and Spa, Carlsbad. Thurs.–Sun. 12 hrs. $145–$195. Contact: CSAAI (714) 828-8022.

CARDIOLOGY

August 13–15—**Critical Care Cardiology.** American College of Cardiology at Ritz-Carlton, San Francisco. Thurs.–Sat. 16.5 hrs. Contact: ACC, 9111 Old Georgetown Rd., Bethesda, MD 20814-1699, (800) 253-4636 ext. 695.

September 10–12—**Coronary Interventions 1998.** Scripps Clinic at Sheraton Grande Torrey Pines Hotel, La Jolla. Wed.–Sat. 28 hrs. Contact: Laurel Steigerwald, Scripps Clinic, Department of Academic Affairs, 403C, 10666 N. Torrey Pines Rd., La Jolla, CA 92037 (619) 554-8556.

September 14–18—**Cardiology Board Review.** UCSF at Cathedral Hill Hotel, San Francisco. $725. Contact: Postgraduate Programs, Box 0656, UCSF, San Francisco, CA 94143-0656.

October 8–10—**The 22nd Annual Seminar: Cardiology Update 1998.** American College of Cardiology at San Francisco. Thurs.–Sat. 12 hrs. $485–$560. Contact: ACC Extramural Programs (800) 253-4636.

October 31—**Update in Electrocardiography and Arrythmias.** UCSF at Radisson Miyako Hotel, San Francisco. Sat. 7.5 hrs. $195. Contact: UCSF (415) 476-5208.

January 7–10, 1999—**NewEra Cardiac Care:Innovation and Technology.** Marriott's Mountain Shadows Resort, Scottsdale Arizona. Sponsored by the Cardiothoracic Research &Education Forum. Contact:Aligned Management Associates, Inc. P.O. Box 23220, San Diego CA 92193 (760) 751-8841. Fax (760) 751-8842. www.amainc.com

January 29–31, 1999—**Clinical Nuclear Cardiology:Case Review With the Experts. Cardiology Update 1998.** American College of Cardiology at San Francisco. Thurs.–Sat. Contact: ACC Extramural Programs (800) 253-4636.

February 18–20, 1999—**19th Annual Pathophysiology & Techniques of Cardiopulmonary Bypass.** San Diego Marriott Hotel & Marina. Sponsored by the Cardiothoracic Research &Education Forum. Contact:Aligned Management Associates, Inc. P.O. Box 23220, San Diego CA 92193 (619) 541-1444 or fax (619) 541-1447 www.amainc.com

DERMATOLOGY

September 19–20—**The Skin A to Z.** UCSF at UCSF Campus. Sat–Sun. 10 hrs. $275. Contact:USCF (415) 476-5808.

January 14–17, 1999—**Practical Dermatology for the Primary Care Physician, San Diego, CA.** Sponsored by Continuing Medical Education Associates. To be held at the Hyatt Regency, La Jolla, San Diego, CA. Method: AV, L, SB, W. Thurs–Sun. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

March 4–7, 1999—**Practical Dermatology for the Primary Care Physician, Orlando, FL.** Sponsored by Continuing Medical Education Associates. To be held at the Buena Vista Palace at Walt Disney World Village, Orlando, FL. Method: AV, L, SB, W. Thus–Sun. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

May 23–26, 1999—**Practical Dermatology for the Primary Care Physician, Las Vegas, NV.** Sponsored by Continuing Medical Education Associates. To be held at the Caesars Palace, Las Vegas, NV. Method: AV, L, SB, W. Sun–Wed. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

EMERGENCY MEDICINE

August 9–12—**Essentials in Emergency Medicine and Urgent Care.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Sun.–Wed. Contact: CMEA P.O. Box 270469, San Diego, CA 92198-2469 or web: http://www.cmea.com.

August 17–18—**High Risk Emergency Medicine.** American College of Emergency Physicians at Marina Beach Marriott, Marina del Rey. Mon.–Tues. 15 hrs. $549. Contact: Center for Emergency Education, 5330 Primrose Dr., Ste. 250, Fair Oaks, CA 95628 (800) 651-CEME.

October 3-7—**National Conference on Wilderness and Travel Medicine.** AmericanCollege of Emergency Physicians at Pare Fifty Five Hotel, San Francisco, CA. 25 hrs. Credit. Contact: (888) 263-6338.

October 8–10—**17th Annual Advances in Pulmonary and Critical Care.** UCSF at Palace Hotel, San Francisco. Thurs.–Sat. 17 hrs. $495. Contact: UCSF (415) 476-5208.

October 19–20—**Trauma Uncensored: 1998.** UC Davis at Hyatt Regency, Sacramento. Mon.–Tue. Contact: (916) 734-5390.

October 19–23—**Emergency Medicine Symposium I.** UCSD at La Jolla Marriott, San Diego. Mon.–Fri. 32 hrs. $495. Contact: OCME (619) 534-3940.

October 26–30—**27th Annual Topics in Emergency Medicine.** UCSF at Radisson Miyako Hotel, San Francisco. Mon.–Fri. 32 hrs. $675. Contact: UCSF (415) 476-5208.

November 9–13—**Emergency Symposium III.** UCSD at La Jolla Marriott, San Diego. Mon.–Fri. 32 hrs. Contact: OCME (619) 534-3940.

December 14-18— **Emergency Symposium II.** UCSD at La Jolla Marriott, San Diego. Mon.–Fri. 32 hrs. Contact: OCME (619) 534-3940.

May 13-16, 1999—**Outdoor Emergency Medicine, Scottsdale, AZ.** Sponsored by Continuing Medical Education Associates. To be held at the Marriott Camelback Inn, Scottsdale, AZ. Method: AV, L, SB, W. Thurs–Sun. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

May 13-16, 1999—**Outdoor Emergency Medicine, Scottsdale, AZ.** Sponsored by Continuing Medical Education Associates. To be held at the Marriott Camelback Inn, Scottsdale, AZ. Method: AV, L, SB, W. Thurs–Sun.

32 hrs credit:AMA, AOA, AAFP. $750. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

ETHICS

October 22–34—**Seventh Annual Symposium on the Design and Methods of Clinical Trials.** UCSF at San Francisco. Thurs–Fri Contact:UCSF Office of Continuing Medical Education. (415) 476-4251.

FAMILY PRACTICE/PRIMARY CARE

August 6–9—**Cardiology in Primary Care.** Sponsored by Continuing Medical Education Associates. Hotel del Coronado, San Diego, CA. Mon.–Thurs. 20 hrs. Credit: AMA, AOA, AAP, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

August 9–12—**Essentials in Emergency Medicine and Urgent Care.** Sponsored by Continuing Medical Education Associates. Hotel del Coronado, San Diego, CA. Thurs.–Sun. 20 hrs. Credit: AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

August 9–12—**Essentials in Emergency Medicine and Urgent Care.** Sponsored by Continuing Medical Education Associates. Hotel del Coronado, San Diego, CA. Thurs.–Sun. 20 hrs. Credit: AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

September 13-15—**Health Care Leadership Institiute Physicans Leadership Program.** Huntington Hotel, San Francisco, CA. Contact Laura Johnson-Morasch California Academy of Family Physicans (CAFP), 114 Sansome Street, Suite 1305, San Francisco, CA 94104-3824. (415) 394-9121 or fax (415 394-9119. email: HCLI@FamilyDocs.org

October 14–16—**13th Annual Primary Care Medicine: Principles and Practice.** UCSF at Cathedral Hill Hotel, San Francisco. Wed.–Fri. 20 hrs. $550. Contact: Postgraduate Programs, Box 0656, UCSF, San Francisco, CA 94143-0656. (415) 476-5208.

October 22–26—**Masters of Medicine.** Sponsored by Continuing Medical Education Associates. Marriott Marquis, New York, NY. Thurs.–Mon. 30 hrs. Credit: AMA, AOA, AAFP. $795. Contact: Victoria Gonzales, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

December 3–4—**Controversies in Women's Health.** UCSF at Cathedral Hill Hotel, San Francisco. Thurs.–Fri. 13 hrs. Credit. $370. Contact: UCSF (415)476-5208.

May 14–18, 1999—**Primary Care Essentials, San Francisco, CA.** Sponsored by Continuing Medical Education Associates. To be held at the Grand Hyatt on Union Square, San Francisco, CA. Method: AV, L, SB, W. Thurs–Sun. 32 hrs credit:AMA, AOA, AAFP. $750. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

GERIATRICS

August 28—**Future Horizons in Home Health Care for Older Americans.** UCLA at Radisson Hotel, Culver City. Fri. 7 hrs. $95. Contact:Jean Abbott, UCLA (310) 312-0531.

September 9–12—**15th Annual Intensive Course in Geriatric Medicine and Board Review.** UCLA at Miramar Sheraton Hotel, Santa Monica. Wed.-Sat. 38 hrs. $720-$795. Contact:Lucio Arruda, 10945 Le Conte Ave. Ste. 2339, Los Angeles, CA 90095-1687. (310) 312-0531.

September 18—**Ethnicity and the Dementias.** UCLA at Queen Mary, Long Beach. Fri. 7 hrs. $95. Contact:Lucio Arruda, 10945 Le Conte Ave. Ste. 2339, Los Angeles, CA 90095-1687. (310) 312-0531.

KEY TO ABBREVIATIONS

DREW:	Charles R. Drew Postgraduate Medical School, Office of Continuing Medical Education, (213) 563-4800.
LLU:	Loma Linda University, Continuing Medical Education Programs, (909) 824-4963.
STAN:	Stanford University, Postgraduate Education, (415) 723-5594.
UCD:	University of California, Davis, Office of Continuing Medical Education, (916) 734-5390.
UCI:	University of California, Irvine, Memorial/UCI Center for Health Education, (714) 824-5926.
UCLA:	University of California, Los Angeles, Continuing Education in Medicine and Health Sciences, (310) 794-2620.
UCSD:	University of California, San Diego, Office of Continuing Medical Education, (619) 534-3940.
UCSF:	University of California, San Francisco, Extended Programs in Medical Education, (415) 476-4251.
USC:	University of Southern California, Postgraduate Division, (800) USC-1119.

November 8–11—**Geriatrics Update 1998.** Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego, CA. Sun.–Wed. 20 hrs. Credit: AMA, AOA, AAFP. $525. Contact: Victoria Gonzales, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

INFECTIOUS DISEASE

September 10—**Immunization Update 1998 Satellite Course.** California Distance Learning Health Network at various sites throughout California. Thurs. 2.5 hrs. Fee varies. Contact:CDLHN (619) 594-3348.

October 29–30—**Globally Emerging Viral Infections.** UCSF at Crowne Plaza Hotel-Union Square, SF. Thurs-Fri. 12 hrs. $415-$470. Contact: UCSF (415) 476-5808.

November 5–8—**Advances in Infectious Disease.** Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego, CA. Thurs.–Sun. 20 hrs. Credit: AMA, AOA, AAFP. $525. Contact: Victoria Gonzales, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200; http://www.cmea.com

November 19—**Preparing for the Coming Influenza Pandemic Satellite Course.** California Distance Learning Health Network at various sites throughout California. Thurs. 2.5 hrs. Fee varies. Contact:CDLHN (619) 594-3348.

December 2–6—**Internal Medicine- 1998 Fall Program.** Sponsored by Continuing Medical Education Associates. Boca Raton Resort and Club, Boca Raton, FL. Wed.–Tues. 30 hrs. Credit: AMA, AOA, AAP, AAFP. $750. Contact: Victoria Gonzales, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

December 3—**Surveillance of Vaccine-Preventable Diseases Satellite Course.** California Distance Learning Health Network at various sites throughout California. Thurs. 2.5 hrs. Fee varies. Contact:CDLHN (619) 594-3348.

December 9—**AIDS-Associated Malignancies: Biology and Clinical Management.** UCSF at Palace Hotel, San Francisco. Wed. Credit 4.5 hours. $135. Contact: UCSF (415) 476-5208.

December 10–12—**Clinical Care of the AIDS Pateient.** UCSF at Palace Hotel, San Francisco. Thurs-Sat. Credit 24 hours. $455. Contact: UCSF (415) 476-5208.

INTERNAL MEDICINE

August 16–21—**New Advances in Internal Medicine:Clinical Applications.** UC Davis at Embassy Suites, on Monterey Bay. Sun-Fri. 31 hrs. $450. Contact:UCD (916) 734-5390.

October 9–13—**Internal Medicine - 1998 Fall Program.** Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego, CA. Fri.–Tues. 30 hrs. Credit: AMA, AOA, AAP, AAFP. $750. Contact: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198-2469. (800) 993-2632 or (619) 674-5200. http//www.cmea.com.

March 19–25, 1999—**Internal Medicine, San Diego CA.** Sponsored by Continuing Medical Education Associates. To be held at the Hotel Coronado, San Diego, CA. Method: AV, L, SB, W. Fri–Thurs. 45 hrs credit:AMA, AOA, AAFP. $895. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

MANAGED CARE

September 10–12—**Management of the Hospitalized Patient in the Managed Care Era.** UCSF at Palace Hotel, San Francisco. 20 hrs. $475. Contact: UCSF (415) 476-5208.

NEPHROLOGY

October 2–8—**13th Comprehensive Nephrology Review Course.** UCLA at Beverly Hilton Hotel, Beverly Hills. Fri-Thurs. 44.5 hrs. $800. Contact: UCLA (310) 794-2620.

NEUROLOGY

October 10—**Brain Attack'98** UCLA at Beverly Hilton Hotel, Beverly Hills,CA. Fee $85. Contact Sheryl Crowley, Office of Continuing Medical Education, UCLA School of Medicine. (310) 794-3324.

OB/GYN

October 23–27—**OB/GYN Review.** Red Lion Hotel, Glendale. $675. Sat.–Tues. 38 hrs. Contact: USC School of Medicine, Postgraduate Division, 1975 Zonal Ave., KAM 307, Los Angeles, CA 90033-1039; Phone

(213) 342-2555 or (800) USC-1119; Fax (213) 342-2152 or (888) 665-8650; email usccme@hsc.usc.edu.

February 11–14, 1999—**Office Gynecology and Women's Health for the Primary Care Physician, San Diego, CA.** Sponsored by Continuing Medical Education Associates. To be held at the Hyatt Islandia, San Diego, CA. Method: AV, L, SB, W. Thurs–Sun. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

February 25–28, 1999—**Office Gynecology and Women's Health for the Primary Care Physician, Orlando, FL.** Sponsored by Continuing Medical Education Associates. To be held at the Buena Vista Palace at Walt Disney World Village, Orlando, FL. Method: AV, L, SB, W. Thurs–Sun. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

OCCUPATIONAL & ENVIRONMENTAL

August 6–7—**Occupational and Environmental Toxicology for the Health & Safety Professional.** University Health Services at Claremont Resort & Spa, Oakland. Thurs.–Fri. 12.5 hrs. $742-$950. Contact: Center for Occupational& Environmental Health, University of California, Berkeley, Richmond Field Station, 1301 S 46th St, Bldg 102, Richmond, CA 94804 (510) 231-5645.

August 6–7—**Synthesizing Office Workstation Ergonomics: Putting it all Together.** University Health Services at Claremont Resort & Spa, Oakland. Thurs.–Fri. 14 hrs. $742-$950. Contact: Center for Occupational& Environmental Health, University of California, Berkeley, Richmond Field Station, 1301 S 46th St, Bldg 102, Richmond, CA 94804 (510) 231-5645.

October 5–9—**Occupational and Environmental Medicine I.** UCSF at Radisson Miyako Hotel, San Francisco. Mon.–Fri. 40 hrs. $725. Contact: Postgraduate Programs, Box 0656, UCSF, San Francisco, CA 94143-0656. (415) 476-5208.

ONCOLOGY

September 11–12—**4th Annual Cancer Research Program.** UC Davis at Cancer Center Auditorium, Sacramento. Fri.–Sat. Contact: UCD (916) 734-5390.

September 24–26—**22nd Annual Physicians Cancer Symposium.** Scripps-Health at Sheraton San Diego Hotel & Marina. Thurs.–Sat. 16.5 hrs. $425–$450. Contact: Stevens Cancer Center, Scripps Memorial Hospital, 9888 Genesee Ave., La Jolla, CA 92037. Tuthanne Crawford (619) 626-6794.

OTOLOGY

November 5–7—**San Francisco Otology and Neurotology Update-1998.** UCSF at Ritz-Carlton Hotel San Francisco. Thurs-Sat. 19 hrs. $475. Contact:UCSF (415) 476-5808.

ORTHOPEDICS

January 14–17, 1999—**Office Orthopedics and Bone Radiology for the Primary Care Physician, San Diego, CA.** Sponsored by Continuing Medical Education Associates. To be held at the Hyatt Regency, La Jolla, San Diego, CA. Method: AV, L, SB, W. Thurs–Sun. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

February 25–28, 1999—**Office Orthopedics and Bone Radiology for the Primary Care Physician, New Orleans, LA.** Sponsored by Continuing Medical Education Associates. To be held at the Royal Sonesta Hotel, New Orleans, LA. Method: AV, L, SB, W. Thurs–Sun. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

February 25–28, 1999—**Office Orthopedics and Bone Radiology for the Primary Care Physician, Las Vegas, NV.** Sponsored by Continuing Medical Education Associates. To be held at the Caesars Palace, Las Vegas, NV. Method: AV, L, SB, W. Sun–Wed. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

PEDIATRICS

September 18–19—**California Society of Pediatric Cardiology.** UC Davis at Seascape Resort, Aptos. Fri.–Sat. Contact: UCD (916) 734-5390.

September 26—**Child's Brain Day-Practical Management of Childhood CNS Disorders.** UCSF at UCSF. Sat. 6.5hrs. $150. Contact:UCSF (415) 476-5808.

January 29–31,1999—**37TH Clinical Conference Pediatric Anesthesiology.** Disneyland Hotel, 1150 W. Cerritos Avenue, Anaheim, CA 92802. Sponsored by The Pediatric Anesthesiology Foudation. $250-$295. Contact David J Steward, M.B., Program Director, Pediatric Anesthesiology Conference Box #3, Childrens Hospital Los Angeles, P.O. Box 54700, Los Angeles, CA 90054. (213) 669-2262 or fax (213) 660-8983.

February 14–17, 1999—**Pediatrics Update 1999, San Diego, CA.** Sponsored by Continuing Medical Education Associates. To be held at the Hyatt Islandia, San Diego, CA. Method: AV, L, SB, W. Sun–Wed. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

February 28–March 3, 1999—**Pediatrics Update 1999, Orlando, FL.** Sponsored by Continuing Medical Education Associates. To be held at the Buena Vista Palace at Walt Disney World Village, Orlando, FL. Method: AV, L, SB, W. Sun–Wed. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

PSYCHIATRY

November 6–8—**44th Annual Group Therapy Symposium.** UCSF at UCSF. Fri–Sun. 20 hrs. $295-$340. Contact:UCSF (415) 476-5808.

RADIOLOGY

October 3–4—**Ultrasound Update: 1998.** UC Davis at Doubletree Hotel, Sacramento. Sat.–Sun. Contact: (916) 734-5390.

RHEUMATOLOGY

September 10–12—**Rheumatology Board Review.** UCSF at Radisson Miyako Hotel, San Francisco. Thurs.–Sat. 20 hrs. $225. Contact: UCSF (415) 476-5208.

SURGERY

September 11–12—**4th Annual Surgical Review Course.** UC Davis at Fairfield. Fri.–Sat. Contact: (916) 734-5390.

September 18—**4th Annual Surgical Review.** UC Davis at TAFT, Fairfield. Fri. Contact: (916) 734-7203.

GENERAL/MULTIDISCIPLINARY

September 3–6—**Growth Hormone Research Society.** UCSF at Marriott Hotel, San Francisco. Thurs.–Sun. Contact: (415) 476-5808.

October 26–28—**Telemedicine IV.** UC Davis at Hilton Hotel, Anaheim. Mon.–Wed. Contact: (916) 734-5390.

May 16–19, 1999—**Alternative Medicine, Scottsdale, AZ.** Sponsored by Continuing Medical Education Associates. To be held at the Mariott Camelback Inn, Scottsdale, AZ. Method: AV, L, SB, W. Sun–Wed. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

LOSS PREVENTION

August 4—**A Quality Improvement Program to Protect Your Medical Practice.** Medical Insurance Exchange of California. at Newark-Fremont Hilton Hotel. Tues. 2 hrs. Free or $40 to non members. Contact: Loss Prevention (800) 227-4527.

August 18—**A Quality Improvement Program to Protect Your Medical Practice.** Medical Insurance Exchange of California. at Embassy Suites Hotel Walnut Creek. Tues. 2 hrs. Free or $40 to non members. Contact: David Carp (800) 227-4527.

September 9—**A Quality Improvement Program to Protect Your Medical Practice.** Medical Insurance Exchange of California. at Corte Madera Best Western Hotel, Corte Madera. Wed. 2 hrs. Free or $40 to non members. Contact: David Carp (800) 227-4527.

October 13—**Preventing "Failure to Diagnose" Malpractice Claims.** Medical Insurance Exchange of California. at Doubletree Hotel, Redding. Tues. Free or $40 to non members. Contact: David Carp (800) 227-4527.

October 20—**A Quality Improvement Program to Protect Your Medical Practice.** Medical Insurance Exchange of California. at Holiday Inn Select, Fairfield. Tues 2 hrs. Free or $40 to non members. Contact: David Carp (800) 227-4527.

November 3—**Medical Records Documentation for Patient Safety and Physician Defensibility.** Medical Insurance Exchange of California. at Santa Fe Bar and Grill, Berkeley. Tues. Free or $40 to non members. Contact: David Carp (800) 227-4527.

November 10—**Preventing "Failure to Diagnose" Malpractice Claims.** Medical Insurance Exchange of California. at San Francisco Medical Society. Wed. Free or $40 to non members. Contact: David Carp (800) 227-4527.

November 11—**Medical Records Documentation for Patient Safety and Physician Defensibility.** Medical Insurance Exchange of California. at Embassy Suites Hotel, Walnut Creek. Wed. Free or $40 for non members. Contact: David Carp (800) 227-4527.

LEARNING SPANISH

July 31–August 3 (Los Angeles); August 28-31(San Diego); September 18–21 (Los Angeles); October 2-5(San Diego); October 23-26(Los Angeles)—**Conversation in Spanish.** Maricopa Health System. 36 hrs. $695. Contact: Rios Associates (520) 881-3295; (619) 218-4875; Fax (520) 325-4258.

HOME STUDY/SELF ASSESSMENT

California Physicians' Legal Handbook Series. California Medical Association. Contact: CMA, PO Box 7690, San Francisco 94120-7690. (800) 882-1262.

Breast Cancer, Early Detection and Control. Texas Medical Association. **CD ROM.** $70. 2 hrs. Contact: Texas Medical Association, (800) 880-1300; http://www.texmed.org/health_science/hs_poep.html

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Second Wednesday of Each Month—**Cardiovascular Education Series.** St Anthony Hospital at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

February 4–6, 1999—**Neurology For The Non-Neurologist.** Hyatt Regency, Cancun Mexico. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

February 5–7, 1999—**Arrhythmias: Interptretation, Diagnosis & Management** MGM Grand, Las Vegas, NV Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

February 12–14, 1999—**Clinical Endocrinology For Primary Care Physicans.** Beaver Run Resort, Breckenridge, CO.Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

February 19–21, 1999—**Managing Respiratory Diseases.** Marriot's Casa Marina,Key West,FL. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

February 25–27, 1999—**Dermatology For The Non-Dermatologist.** Atlantis Paradise Resort, Bahamas. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

February 26–28, 1999—**Coronary Heart Disease Update.** Hilton Tapatio Cliffs, Scottsdale, AZ. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

March 12–14, 1999—**Dermatology For The Non-Dermatologist.**Riviera Hotel & Casino, Las Vegas, NV. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

March 25–27, 1999—**Neurology For The Non-Neurologist.** Grand Beach Resort, St. Thomas, USVI. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

March 25–27, 1999—**Clinical Endocrinology For Primary Care Physicans.** Marriott's Beach Resort, St. Grand Cayman. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

March 26–28, 1999—**Managing Respiratory Diseases.** Buena Vista Palace,Orlando,FL. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 8–10, 1999—**Coronary Heart Disease Update.** Hyatt Regency, Aruba Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 8–10, 1999—**Clinical Endocrinology For Primary Care Physicans.** The Westin Resort, St John, USVI. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 9–11, 1999—**Arrhythmias: Interptretation, Diagnosis &Management** Hilton Tapatio Cliffs, Scottsdale, AZ. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 9–11, 1999—**Neurology For The Non-Neurologist.** Marriott's Casa Marina, Key West, FL. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 23–25,1999—**Managing Respiratory Diseases.** Bally's, Las Vegas, NV. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 23–25,1999—**Dermatology For The Non-Dermatologist.** Parc Fifty-five, San Francisco, CA. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 30–May 2, 1999—**Dermatology For The Non-Dermatologist.** South Sea Plantation, Captiva Island, FL. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 30–May 2, **Clinical Endocrinology For Primary Care Physicans.** Hyatt Regency, New Orleans, LA. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

May 14–16, 1999—**Managing Respiratory Diseases.** Hilton Resort, Hilton Head, SC. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

May 14–16, 1999—**Neurology For The Non-Neurologist.** Bally's, Las Vegas, NV. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

IDAHO

The listing of continuing medical education programs in Idaho is compiled by the Ada County Medical Society. To list CME programs here, please send information at least two months in advance to: Ada County Medical Society, Inc. 305 W. Jefferson, PO Box 2668, Boise, Idaho 83701. (208) 336-2930.

Brochures, course information, and registration forms are available from the contact person or organization.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

July 30–August 2—**Imaging in Santa Fe.** La Fonda Hotel, Santa Fe, New Mexico. Credit 20 hrs. AMA. $695. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

August 3–6—**Point-Counterpoint: Breast Imaging in Transition.** Eldorado Hotel, Santa Fe, New Mexico. Credit Approx. 26 hrs.AMA. $650. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email; webmaster@ryalsmeet.com.

October 12–15—**Neuroradiology for the Practicing Radiologists--The Robert Jahnke Memorial Course.** Hotel Loretto, Santa Fe, New Mexico. Approx. 20 hrs.AMA. $695. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

Every First and Third Tuesday—**Building and Implementing Clinical Practice Guidelines at the Point of Care.** Contact: Thomas A. Naegele, DO, (505) 275-7267.

Satellite Courses

Contact: Joe Treat or Jim Cato, Immunization Program, (505) 827-2366

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

July 11–18—**Update in Clinical Immunology, Microbiology, and Infectious Diseases.** Snow King Resort at Jackson Hole, Wyoming. 25 hrs Credit AMA. Contact: (801) 581-8664; fax (801) 581-3647; email Rosalie.Lammle@hsc.utah.edu.

July 12–18—**Summer Meeting on Neuroradiology and Musculoskeletal Imaging.** Bishops Lodge, Santa Fe, New Mexico. Credit 30 hours AMA. Contact: (801) 581-8664; fax (801) 581-3647; email: Rosalie.Lammle@hsc.edu.

August 19–21—**Clinical Computing for Integrated Health Care Networks.** Yarrow Hotel and Conference Center, Park City. Credit 21 hours AMA. Contact: (801) 581-8664; fax (801) 581-3647; email: Rosalie. Lammle@hsc.edu.

August 19–22—**Seminars in Clinical Computing: Update 1998.** Park City. 19 hrs. Credit: AMA, AAFP, nursing CEU. Contact: University of Utah Office of CME, 50 N. Medical Dr., Salt Lake City, UT 84132. (801) 581-8664; fax (801) 581-3647; email: Rosalie.Lammle@hsc.utah.edu.

September 11—**Ophthalmology--Clinical Faculty Day.** John Moran Eye Center, Salt Lake City. 7 hrs. Credit AMA. Contact: (801) 581-8664; fax (801) 581-3647; email: Rosalie.Lammle@hsc.utah.edu.

September 17–20—**Innovative Techniques in Plastic Surgery.** Wort Hotel, Jackson, Wyoming. 16 hrs. Credit AMA. Contact: (801) 581-8664; fax (801) 581-3647; email: Rosalie.Lammle@hsc.utah.edu.

September 29–October 3—**International Workshop on Magnetic Resonance Angiography**. Prospector Square Hotel and Conference Center, Park City. Not designated Category 1. Contact: (801) 581-8664; fax (801) 581-3647; email: Rosalie.Lammle@hsc.utah.edu.

October 2–3—**Western Intermountain Neurological Organization.** University Park Hotel, Salt Lake City. 12 hrs. Credit AMA. Contact: (801) 581-8664; fax (801) 581-3647; email: Rosalie.Lammle@hsc.utah.edu.

October 9–11—**Intensive Interactive Head and Neck Imaging Course.** University Park Hotel, Salt Lake City. 23 hrs. Credit AMA PRA.October 6-8, Preconference mini-fellowship (limited to course attendees), University of Utah School of Medicine, Department of Radiology. Contact: (801) 581-8664; fax (801) 581-3647; email: Rosalie.Lammle@hsc.utah.edu.

MEDICAL GRAND ROUNDS

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics.** Contact: UUSM.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

July 10–12—**3rd Annual Laser and Facial Plastic Surgery Symposium With Live Surgery Observation.** Presented by Wayne F. Larrabee, Jr, MD. Swedish Medical Center, Glaser Auditorium, Seattle. 17 hrs. Contact: (206) 386-2755.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Ave, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 S Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 340-2058.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Ste 1100, Seattle, WA 98121. (206) 441-9762.

OTHER CME OPPORTUNITIES

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE. June 26–28, 1998—**Fortieth Annual Scientific Meeting of The American Association for the Study of Headache**. Sheraton Palace, San Francisco. Contact: (609) 845-1720.

AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE. November 6–8, 1998—**Scottsdale Headache Symposium**. Scottsdale at Marriott's Camelback Inn Resort & Spa. Contact: (609) 845-1720.

The Atopy Syndrome in the Third Millenium. October 2–3, 1998, Zurich, Switzerland, on the occasion of the 50th anniversary of the allergy unit at the Dept of Dermatology, University Hospital, Zurich, and in collaboration with the European Academy of Allergology and Clinical Immunology. Contact: Prof. Dr. B. Wüthrich, Zurich, 41-1-255-3079, fax 41-1-255-4431.

Breast Imaging Today and Tomorrow. November 2–5, 1998. The Ritz-Carlton Resort Hotel, Naples Florida. Credit 26 hrs. AMA. $650. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

Internal Derangements of Joints October 9–11, 1998. The Westin River North, Chicago, Illinois. Credit 19 hrs. AMA. $695. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

THE INTERNATIONAL SKELETAL SOCIETY.- September 9–12, 1998—**25th Annual Refresher Course: Diagnosis & Management of Musculoskeletal Disorders**. Jury's Hotel, Dublin, Ireland. Credit 25 hrs. AMA. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

Mt. Sanai 1998 Body Imaging Update. October 10–13, 1998. The Plaza Hotel, New York, NY. Credit 22.5 hrs. AMA. $695. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

Musculoskeletal MR. October 22–25, 1998. The Westin Resort Hotel, Hilton Head, South Carolina. Credit 18 hrs. AMA. $650. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

NOTICE

State Associations should send their CME listings for publication to:

Allison Spearman, Managing Editor
Western Journal of Medicine
1224 W Main St, Ste 200
Charlottesville, VA 22903-2858

(804) 979-8034 • Fax (804) 979-4025 • wjm@cjp.com

Articles

Insight on Emphysema—The First 300 Cases of Surgical Treatment

RICHARD J. FISCHEL, MD, PhD, ROBERT J. MCKENNA, JR, MD, *Los Angeles, California,* ARTHUR GELB, MD, *Lakewood, California,* NARINDAR SINGH, MD, *Orange, California, and* MATTHEW BRENNER, MD, *Irvine, California*

Our experience with lung volume reduction surgery for emphysema now encompasses more than 300 cases, including several prospective trials. We have a 3.5% operative mortality rate and, with aggressive use of Heimlich valves over the past 6 months, an average hospital length of stay of 8 days. Proper patient selection is essential and can be based primarily on results of pulmonary function tests (PFTs), ventilation/perfusion (V/Q) scans, and computed tomography (CT) scans. We have found that bilateral is more effective then unilateral staple lung volume reduction surgery, which is in turn better than unilateral laser surgery. In patients with bilateral upper lobe disease, average FEV_1 (forced expiratory volume in a 1-second interval) improvement is 82%; overall, it is 61% (range –33 to 217%). We conclude that lung volume reduction surgery can be performed safely with acceptable mortality and excellent clinical results in properly selected, motivated patients.

(Fischel RJ, McKenna RJ, Gelb A, Singh N, Brenner M. Insight on emphysema: the first 300 cases of surgical treatment. West J Med 1998; 169:74–77)

Surgical therapy for emphysema, although in its infancy, has shown great promise as a treatment for selected patients with end stage bullous lung disease.[1–3] First performed in the late 1950s by Dr. Otto Brantigan,[4] the surgical approach underwent renewed popularity after initial reports from Dr. Joel Cooper in 1994 indicated a zero percent mortality rate and significant measurable improvement in pulmonary function physiology.[5] In the subsequent flurry of procedures were performed at numerous institutions in a variety of different techniques—with a wide range of morbidities, mortalities, and overall results. Many new questions arose in regard to patient selection, appropriate preoperative preparation, and choice of surgical procedure. To address some of those questions, we have performed both randomized prospective and retrospective studies comparing surgical techniques, staple line buttressing materials, and adjunctive therapeutic procedures and experiments designed to elucidate the physiologic mechanism of improvement after lung reduction surgery. Here we present the lessons learned from evaluation of more than 300 patients involved in these studies.

In every case, patients gave informed consent regarding their inclusion in the clinical trials. Each trial was approved before patient enrollment by the regulating board at the hospital where it was performed. Several of these studies have been presented in great detail elsewhere[6–9] and will be summarized here.

Operative Technique

When our surgical treatment for emphysema program was initiated (May 1994), there were two main schools of thought as to the best procedure for the disease. Unilateral laser bullectomy as popularized by Dr. A. Wakabayashi[10] had been performed on more than 500 patients, with reports of significant improvement in pulmonary function. Dr. Cooper's data[5] favored bilateral resectional therapy through a median sternotomy.

We conducted a randomized prospective trial of laser vs resectional therapy using unilateral thoracoscopic techniques. In each laser case, a contact YAG laser applied an average of 24,900 joules to the entire lung surface. In each staple case, between seven and 10 bovine pericardium–reinforced ELC 60 staple firings were applied to resect 20 to 30% of the lung in the most severely affected emphysematous areas of the worse lung. In all, 72 patients were randomly assigned to either Nd-YAG contact tip laser therapy (n = 33) or staple lung volume reduction (n = 39).

The unilateral stapling procedure achieved a significantly greater improvement in FEV_1 (forced expiratory

From the Lung Center, Chapman Medical Center, Orange, California.
Reprint requests to Richard J. Fischel, MD, PhD, 8635 W 3rd St, #975W, Los Angeles, CA 90048.

TABLE 1.—*Results of Three Procedures for Lung Volume Reduction Surgery*

Procedure	n	Improvement in FEV_1 at 6 Months (%)	Patients Clinically Improved (%)	Patients With Late Pneumothorax (%)	Patients Off Oxygen (%)	Patients Off Prednisone (%)	1-Year Mortality in High-Risk Patients (%)
Unilateral Laser	33	13	24	18	52	—	—
Unilateral Staple	76	33	56	0	56*	54	17
Bilateral Staple	122	61	88	0	86*	85	1.1

*If Preoperative pO_2 > 50 mmHg on room air.

volume in a 1-second interval) than laser bullectomy. The mean improvement of patients' FEV_1 at 6 months was 0.22 L (mean ± SE, 32.9 ± 4.8%) for the staples and 0.09 L (13.4 ± 5.5% ± SE) for the laser (P = 0.01). The improvement from baseline in forced vital capacity (FVC) of the staple patients was also significant (P < 0.006). The mortality rate, hospital length of stay, air leak duration, operating time, and surgical take-back rate for bleeding or massive air leak were not significantly different between the two groups. On the other hand, delayed pneumothorax after hospital discharge occurred in 18% of the laser bullectomy patients compared with 0% in the staple patients (P = 0.005). This phenomenon has been confirmed by the work of Little et al,[1] who reported delayed pneumothorax after laser treatment in 11 of 55 patients (20%); similar results have been reported elsewhere.[2,3] The addition of laser treatment to a unilateral staple operation[2] resulted in no additional improvement in pulmonary function (FEV_1 increased 34 vs 33%, laser vs no laser).

Compared with the laser patients, a greater number of staple patients showed improvement in their dyspnea index (66 vs 24% for laser patients) (P = 0.003). At 6 months, 87.5% of staple patients had been weaned off oxygen, vs 52% of laser patients (P = 0.02). Also, a greater number of patients reported clinical improvement on a quality-of-life questionnaire administered after the staple procedure. The results of these unilateral studies, combined with the superior results Cooper reported with a bilateral staple procedure, led us to adopt the staple technique instead of the laser technique for lung volume reduction surgery.

Unilateral vs Bilateral

The next study involved 166 consecutive patients who underwent either unilateral (n = 87) or bilateral (n = 79) thoracoscopic staple lung volume reduction procedures. In this series, there was no statistically significant difference in operative mortality (3.5 vs 2.5%, respectively), mean length of stay (11.4 vs 10.9 days), or morbidity between the groups. At 6 months, 36% of the unilateral and 68% of the bilateral patients were weaned from oxygen (P < 0.01), and prednisone independence was achieved in 54 vs 85% (P = 0.02).

Bilateral thoracoscopic lung reduction achieved a mean FEV_1 improvement of 72% patients with residual volumes > 200% predicted, comparable to Cooper's series of bilateral procedures in similarly hyperinflated patients via sternotomy. Overall bilateral lung volume reduction surgery achieved a mean improvement in FEV_1 of 57% compared with 31% for unilateral reduction procedures (P < 0.01). Also, 44% of unilateral surgery patients had postoperative Grade 3 or 4 dyspnea compared with 12% of bilateral surgery patients. One-year mortality (including operative mortality) was 5.1% in the bilateral group and 17% in the unilateral group (P < 0.001). The deaths occurred primarily from respiratory failure in the high-risk unilaterally treated patients, i.e., those older than 75 years and those with preoperative pO_2 < 50 or FEV_1 < 500 mL.

Multivariant analysis of the unilateral vs bilateral groups failed to identify statistically significant differences in preoperative variables. Several highly suggestive trends did become apparent, however. Patients with hyperinflation showed more improvement in both the unilateral and bilateral groups. Patients with upper lobe disease did better than those with lower lobe disease, who did better than those with diffuse disease (target areas in multiple lobes). When operative factors were analyzed, the amount of lung resected (in grams) correlated positively with improvement in FEV_1, while dense adhesions over 50% of the thoracic space had a negative correlation with FEV_1 improvement.

Some patients achieved significant improvement with unilateral lung volume reduction surgery, but we were unable to find any preoperative factors that would have identified those patients. Because the bilateral operation results in greater overall improvement in every measurable patient parameter, and without additional morbidity and mortality, we are convinced that bilateral lung volume reduction surgery, when achievable, is the operation of choice. The significant difference in 1-year mortality rates was found to be, almost exclusively, a factor of the deaths secondary to respiratory failure in the severely compromised patients (FEV_1 < 500 mL, pO_2 < 50, age > 75) after unilateral surgery. Because the two groups were well matched by all preoperative measurements, we concluded that the bilateral procedure is especially important for those high-risk patients. The unilateral procedure is reserved for patients with contraindications to bilateral surgery, such as prior thoracotomy or pleurodesis. Results of the two studies, staple vs laser and bilateral vs unilateral, are summarized in Table 1.

Patient Selection

Patient selection is of critical importance. Commonly accepted selection criteria include the following:

1. Severe obstructive airway disease, $FEV_1 < 35\%$ despite maximal medical therapy.
2. Severe air trapping with elevated total lung capacity (TLC) and residual volume.
3. Evidence for heterogeneous bullous emphysema on CT scan, preferably upper lobe targets.

The issues of age, ambulatory status, CO_2 retention, and pulmonary artery hypertension are less clearly defined.

To further define selection criteria, we retrospectively evaluated 154 consecutive patients who underwent bilateral thoracoscopic staple lung volume reduction surgery. Our preconceived notions of acceptability influenced patient selection such that only 31% of patients evaluated (154 of 487) were accepted as surgical candidates. The reasons for rejection included lack of heterogeneous emphysema (212), medical contraindications (88), hypercapnia (20), uncontrolled anxiety or depression (10), death (2), and pulmonary artery hypertension (1).

Preoperative parameters were compared with clinical outcome (e.g., change in FEV_1, dyspnea index). We found that one of the strongest predictors of good outcome was a heterogeneous upper lobe pattern on CT and V/Q scans, with a mean improvement in FEV_1 of 68.8% vs 36.8% for lower lobe disease. Quantitative perfusion scans also played a critical role in identifying target areas of resection and determining eligibility for surgery. If no area of severe lung destruction or decreased perfusion could be identified (diffuse emphysema), the patient was deemed a nonsurgical candidate.

The retrospective study provided many other insights. First, older patients—those over age 75 treated with a bilateral operation—did very well. This is in direct contrast to the increased risk these patients encountered with a unilateral operation. None of the 17 patients ages 75 to 82 died, their mean increase in FEV_1 was 90%, and overall condition and pulmonary function improved in 14 of them. Second, 14 patients with hypercarbia (mean $pCO_2 = 60$) not only increased their FEV_1 an average of 84% but also lowered their pCO_2 to a postoperative mean of 42.8 mmHg and improved their dyspnea scale measurements from 3.4 to 2.4. These patients were selected because of the ability to decrease their CO_2 with strenuous preoperative rehabilitation, although not to levels less than 55 mmHg. Patients with very low FEV_1 (<500 mL) had an 11% operative mortality rate (five of 55), but the survivors had a mean 106% improvement in FEV_1 and a significant decrease in the dyspnea scale, from 3.18 to 1.16.

Patients with significant preoperative hypoxia ($pO_2 < 50$) had a mean increase in FEV_1 of 98% and a reduction in dyspnea scale, although nine of the 13 patients continued to require supplemental oxygen 6 months after surgery. Patients with severe hypoxemia at rest (requiring 4 L nasal cannula O_2 preoperatively) had minimal to no improvement (four of 8 patients) in dyspnea index despite a mean 60% improvement in FEV_1. All eight continued to require oxygen.

Eight patients on high-dose prednisone (>20 mg/day) had a 45% increase in FEV_1 and decreased dyspnea scale from 3.56 to 2.2.

Other Studies

The occurrence of air leaks after lung reduction remains a major source of morbidity despite the advent of buttressing materials.[11,12] Although longstanding surgical thinking would dictate that suction is required to create negative intrathoracic pressure and inflate a collapsed lung, this is not the case in lung volume reduction surgery. In fact, the suction appears to maintain air flow through the leaking lung and subsequently slow healing. We began treating all lung volume reduction surgery patients with "water seal only" postoperatively in early 1995. The patients appear to tolerate an apical air space from 1.5 to 7 cm without distress. Several early patients were switched to Heimlich valves to allow easy ambulation and did well, their air leaks healing and their lungs reexpanding. In a subsequent study, 25 of 107 patients (24%) experienced a prolonged air leak (>5 days) after lung reduction surgery for emphysema. The chest drainage system was replaced by a Heimlich valve to facilitate ambulation, earlier hospital discharge, and possibly healing of the air leak. Mean hospital stay was reduced 46%, to 9.1 days. The chest tubes were removed an average of 7.7 days after discharge with no ill effects noted. There were no mortalities, empyemas, or pneumonias. We concluded that the aggressive use of Heimlich valves to treat postoperative air leaks, as well as avoidance of postoperative suction, increased mobility and patient acceptance and decreased hospital length of stay. It also eliminated returns to the operating room for pleural tents or attempts to find and suture air leaks.[13]

Mechanics of Improvement

We prospectively studied the mechanism of air flow limitation in 12 consecutive patients undergoing bilateral staple lung volume reduction procedures. Patients were studied preoperatively, intraoperatively under general anesthesia with paralysis, and postoperatively. We found a significant increase in lung elastic recoil at total lung capacity as well as maximal expiratory air flow in every patient. The measured increase was detectable immediately after resection in the operating room and appeared to be a result of the change in lung elastic recoil and not chest wall compliance, where no change was realized. We have now followed these patients for up to 1 year, and the findings remain consistent, although there does appear to be some deterioration toward preoperative levels over time.[15]

Conclusions

The optimal surgical technique for lung volume reduction surgery is the bilateral staple procedure. Older patients (>75 years), patients with elevated pCO_2, and patients on high-dose steroids could all receive signifi-

TABLE 2.—*Selection Criteria for Lung Volume Reduction Surgery*

Criteria	*Optimal Candidate*	*Possible Candidote*	*Noncandidate*
Symptoms	Moderate	Severe	Minimal
Anxiety	Controlled	Moderate	Severe
Depression	Controlled	Moderate	Severe
Age	<75 years	>75 years	—
Oxygen requirements	< 4 L	—	>4 L
pO_2	>50	40–50	<50
pCO_2	<55	>55	—
Pattern of Disease	Upper lobe	Lower lobe	Diffuse
FEV_1	20–40%	<20%	>50%
Total lung capacity	>120%	95–120%	<95%
Residual volume	>250%	150–250%	<150%

cant benefit from lung volume reduction surgery, and there appears to be no lower limit of FEV_1 for successful outcome. Patients with severe hypoxemia should probably not undergo lung volume reduction surgery. Patients with hyperinflation respond well to lung volume reduction surgery, although severe hyperinflation does not seem to be a requirement for significant improvement any more than moderate hyperinflation (residual volume 150 to 250%). Overall, upper lobe disease responds best, although some patients with lower lobe disease have significant improvement in dyspnea indexes despite smaller changes in FEV_1. Severe anxiety, severe depression, and failure to undergo rehabilitation correlate strongly with bad results. The selection criteria are summarized in Table 2.

Lung volume reduction surgery can provide substantial improvement for selected patients in quality of life and pulmonary function. The bilateral staple operation (either open or closed) can be performed with acceptable morbidity and mortality even in the most severely disabled patients. Long-term results and impact on survival require further studies, which should also further define patient selection criteria.

REFERENCES

1. Little AG, Swain JA, Nino JJ, Nino RD, Schlachter MD, Barcia TC. Reduction pneumoplasty for emphysema. Early results. Ann Surg 1995; 222:365–371

2. Eugene J, Ott RA, Gogia HS, Dos Santos C, Zeit R, Kayaleh RA. Video thoracic surgery for treatment of end stage bullous emphysema and chronic obstructive pulmonary disease. Am Surg;1995;61(10):924-6

3. Keenan RJ, Landeneau RJ, Sciurba FC, et al. Unilateral thoracoscopic surgical approach for diffuse emphysema. J Thorac Cardiovasc Surg;1996;111:308-15

4. Brantigan OC, Mueller E. Surgical treatment of pulmonary emphysema. Am Surg;1957;23:709-804

5. Cooper JD, Trulock EP, et al. Bilateral pneumonectomy (volume reduction) for chronic obstructive pulmonary disease. J Thorac Cardiovasc Surg; 1995; 109(1) 106-16

6. McKenna RJ, Brenner M, Gelb A, et al. A randomized prospective trial of stapled lung reduction versus laser bullectomy for diffuse emphysema. J Thorac Cardiovas Surg;Feb, 1996:111:2:317-322

7. McKenna RJ, Brenner M, Fischel RJ, et al.Should lung reduction surgery for emphysema be unilateral or bilateral. J Thorac Cardiovasc Surg;Vol 110, Number 4

8. McKenna RJ, Brenner M, Fischel RJ, Yoong MI. Patient selection criteria for lung volume reduction surgery. J Thorac Cardio Surg ; Vol. 114:6:Dec 1997; p957-67

9. Gelb A, McKenna RJ, Brenner M, Fischel RJ, Baydor A, Zamel N. Contribution of lung and chest wall mechanics following emphysema resection. Chest; July, 1996;Vol 110:11-17

10. Wakabayashi, A. Thoracoscopic laser pneumoplasty in the treatment of diffuse bullous emphysema. Ann Thorac Surg;1996;60:936-40

11. McKenna RJ, Fischel RJ, Brenner M, Gelb A. Use of the Heimlich valve to shorten hospital stay after lung reduction surgery for emphysema. Ann Thorac Surg;1996;61:1115-7

12. Cooper JD. Technique to reduce air leaks after resection of emphysematous lung. Ann Thorac Surg;1994;57(4):1038-9

13. Fischel RJ, McKenna RJ, Brenner M, Gelb A. Bovine pericardium versus bovine collagen to buttress staples for lung reduction surgery. Ann Thorac Surg; 1998;65:217-9

14. Gelb A, Zamel N, McKenna RJ, Brenner M. Mechanism of short term improvement in lung function following emphysema resection. Am J Resp Crit Care; 1996;154, pp 945-951

15. Gelb A, Brenner M, McKenna RJ, Zamel, N, Fischel RJ, Epstein JD. Lung function 12 months following emphysema resection. Chest;Dec, 1996;Vol 110:1407-1415

16. Fischel RJ, McKenna RJ, Peters H. Thoracoscopic stapled lung reduction surgery for emphysema. Surgical Rounds; July, 1996:272-278

Articles

Splenomegaly in 2,505 Patients at a Large University Medical Center From 1913 to 1995

1913 to 1962: 2,056 Patients

ROBERT A. O'REILLY, MD, *San Francisco, California*

This is part I of a two-part article. See pages 88–97 for part II.

Splenomegaly was studied retrospectively at the University of California, San Francisco, School of Medicine, on all patients (N = 2,056) for the years 1913 to 1962. The patients were classified into several diagnostic groups, and these groups were tested for statistical significance (χ^2) with many clinical and laboratory variables to determine their predictive value. Hematologic disorders were associated with 57% of cases of splenomegaly and 81% of cases of massive splenomegaly. Among patients with splenomegaly, 19% had infectious diseases, 11% had hepatic diseases, and 9% had congestive or inflammatory disorders. The residual 4% were considered to have primary splenic disorders or a disorder of unknown cause. The commonest diseases associated with splenomegaly were hematologic (acute and chronic leukemias), infectious (malaria, endocarditis, and tuberculosis), hepatic (chronic liver disease), congestive (congestive heart failure), inflammatory (thyrotoxicosis), and other (cancers not metastatic to the spleen). The diseases most frequently associated with massive splenomegaly were the chronic leukemias. The disease with the highest incidence of massive splenomegaly was myelofibrosis (23 of 29 patients, 78%). Splenectomy was performed in 154 patients (7%), primarily for hematologic amelioration and hepatic hypersplenism. Hematologic diseases showed significant associations with lymphadenopathy, generalized lymphadenopathy, massive splenomegaly, and cytoses (*P* .001) and with progressive splenic enlargement (*P* < .02). Infectious diseases showed significant association with fever, and hepatic diseases showed significant association with abnormal results of liver function tests (*P* < .001). The findings of this retrospective study should be validated prospectively.

(O'Reilly RA. Splenomegaly in 2,505 patients at a large university medical center from 1913 to 1995. 1913 to 1962: 2,056 patients. West J Med 1998; 169:78–87)

The subject of splenomegaly in hospital-based patients from developed countries has elicited few published articles in the past 50 years or more. Splenomegaly is a diagnostic challenge because almost all the associated diseases are extrinsic to the spleen.[1] The various diseases associated with splenomegaly depend greatly on the geographic and clinical locale and perhaps even on the time of occurrence—for example, before or after the development of antibiotics.[2] The only general analyses of splenomegaly from a developed country were two office-based studies performed decades ago in which no diagnosis was established in more than 25% of patients.[3,4] Recent evaluations of splenomegaly come mostly from developing countries[2]; these reports emphasize infectious diseases or are focused on massive splenomegaly, especially its surgical aspects.[5] The only study of splenomegaly in hospital-based patients from a developed country, the United States, analyzed patients at a county hospital from 1983 to 1993.[6] Furthermore, the changing causes of splenomegaly extending back to before the antibiotic era from one clinical site have never previously been reported. This retrospective study of splenomegaly in hospital-based patients of a developed country from one university medical center over an 82-year period attempts to overcome many of these limitations.

The University of California, San Francisco, School of Medicine (UCSF) has retained all of its medical records since 1913, allowing a uniform study of all the

From the Departments of Medicine, University of California, San Francisco, School of Medicine; Stanford University Medical Center, Palo Alto; and Santa Clara Valley Medical Center, San Jose, California.

Reprint requests to Robert A. O'Reilly, MD, 751 S Bascom Ave, San Jose, CA 95128.

ABBREVIATIONS USED IN TEXT

ALL = acute lymphoblastic leukemia
CHF = congestive heart failure
CLL = chronic lymphocytic leukemia
CML = chronic myelocytic leukemia
RBCs = erythrocytes [red blood cells]
UCSF = University of California, San Francisco
WBCs = leukocytes [white blood cells]

patients coded for splenomegaly over time. Those patients were retrospectively evaluated as the basis of this study. The various diseases found with splenomegaly were placed in diagnostic groups.[1] The association of these diagnostic groups with several clinical and laboratory features was analyzed for statistical significance to determine the diagnostic groups' predictive value.

Patients and Methods

Patient Demographics

All hospital records at UCSF for patients of any age diagnostically coded as splenomegaly from 1913 through 1962 were reviewed. *Splenomegaly* was defined as an enlarged spleen determined by one of the following: palpable on abdominal examination by at least two clinicians or noted on two written observations, more than 12 cm in length on a radiographic report, or greater than 250 grams wet weight of an excised spleen from an operation or autopsy. A total of 2,325 patients were coded with splenomegaly; 269 medical records (11.6%) of patients with splenomegaly could not be found. Therefore, the study was based on records of the remaining 2,056 patients. The incidence of splenomegaly in this study was 2,056 patients in about 220,000 admissions to UCSF, or 0.9%.

Clinical and Laboratory Features

The medical records were analyzed for the following clinical features: splenomegaly, massive splenomegaly, progressive splenic enlargement, hepatomegaly, lymphadenopathy, generalized lymphadenopathy, fever, and left upper quadrant pain and tenderness. *Hepatomegaly* was defined as a liver span of at least 12 cm in the right midclavicular line or any detection of the liver in the epigastrium. *Lymphadenopathy* was defined as enlarged lymph nodes detected during physical examination or imaging in at least two body sites and generalized lymphadenopathy if detected in more than two body sites. *Fever* was defined as a body temperature of greater than 38.0°C on two successive days. *Left upper quadrant pain or fullness* was defined as a patient's stated perception of pain or fullness in that area. *Left upper quadrant tenderness* was defined as the physician's perception of tenderness on palpation of that area or direct splenic tenderness. *Massive splenomegaly* was defined as a spleen palpable more than 15 cm below the left costal margin or below or at the level of the umbilicus during physical examination, or greater than 18 cm in length on a radiographic report, or more than 1,500 grams wet weight of an excised spleen from a surgical procedure or autopsy. In children, the weight of the spleen was normalized to a body weight of 70 kg (154 lb).

Patients' medical records were analyzed for the following laboratory features: cytopenia, such as thrombocytopenia and leukopenia, either alone or in combination; cytoses such as erythrocytosis, leukocytosis, or thrombocytosis, or a pronounced leftward shift of the neutrophilic leukocytes (WBCs) of the peripheral blood or the presence of nucleated erythrocytes (RBCs) on the peripheral blood smear, or a reticulocyte count of 0.10 (10% of RBCs) or greater than 200×10^9 per liter; and abnormal results on liver function tests. Anemia by itself was not evaluated as a cytopenia because of the high incidence of chronic anemia in hospital inpatients. A *pronounced leftward shift of the neutrophilic WBCs* was defined as myelocytes, promyelocytes, or myeloblasts on the peripheral blood smear. *Leukopenia* was defined as a WBC count of less than 4.0×10^9 per liter (4,000 per (l), thrombocytopenia as a platelet count of 120×10^9 per liter (120,000 per (l), leukocytosis as a WBC count of 15.0×10^9 per liter (15,000 per (l), thrombocytosis as platelet count of greater than 500×10^9 per liter (500,000 per (l), and erythrocytosis as a hematocrit of greater than 0.52 (52%). Stricter criteria were applied because mild degrees of leukopenia and thrombocytopenia are common in hospital inpatients. *Abnormal results of liver function tests* were defined by the presence of at least two of the following laboratory findings in a patient: an elevated total serum bilirubin level (>26 μmol per liter [>1.5 mg per dl]), an elevated serum alkaline phosphatase level (>1.5 times the upper limits of normal), or a decreased serum albumin value (<34 grams per liter [<3.4 grams per dl]). Other common tests of hepatic function that exist today were not available before 1937. For more recent patients, the following tests were usually available: an increased aspartate or alanine aminotransferase level (>2 times the upper limits of normal), a prolonged prothrombin time (>15 seconds), or a prolonged partial thromboplastin time (>35 seconds). When two or more disorders associated with splenomegaly existed in a patient, only the most likely disease was recorded.[4]

Diagnostic Classification and Statistical Analysis

The patients with splenomegaly were classified into several diagnostic groups: infectious diseases, hematologic disorder, hepatic disease, congestive or inflammatory disease, primary splenic disorder, and other. To determine the positive and negative associations of the clinical and laboratory features with the diagnostic groups, comparisons of these variables were made by χ^2 analysis. Differences at the .05 level were considered significant.

Results

A palpable spleen was regarded as splenomegaly; no patient was found in whom a left upper quadrant mass displaced a normal-sized spleen. Patients ranged in age from newborn to 87 years, with a median age of 34. Of the 2,056 patients, 23% were younger than 18 years,

TABLE 1.—*All Causes of Splenomegaly and Massive Splenomegaly by Diagnostic Group (N = 2,056)* *

	Total Splenomegaly, %		Subtotal With Massive Splenomegaly, %		
Diagnostic Group	1913 to 1936 (n = 621)	1937 to 1962 (n = 1,435)	1913 to 1936 (n = 118)	1937 to 1962 (n = 334)	% of Each Diagnostic Group†
Hematologic	34	67	69	84	31
Infectious	43	8	17	3	8
Hepatic	10	11	8	9	17
Congestive or inflammatory	9	9	2	1	3
Other	2	2	1	0	2
Primary splenic	1	2	2	3	36
Unknown	1	1	1	0	5
Total	100	100	100	100	22

*Data are derived from patients from the earlier series (1913 to 1936) and the later series (1937 to 1962) at the University of California, San Francisco, School of Medicine.
†% of each diagnostic group indicates massive splenomegaly as a percentage of the total number of patients with splenomegaly.

11% were younger than 2 years, 2% were older than 70 years, and 1% were older than 80 years. Sixty-one percent of the patients were male. All the patients were admitted to the hospital, which allowed the assignment to a diagnostic group of all but 21 patients (1%). Splenomegaly was detected by physical examination in 89% of the patients, by autopsy alone in 6%, and by radiographic examination alone in 5%.

Table 1 shows all the patients with splenomegaly and massive splenomegaly by diagnostic group. The commonest diagnostic group associated with splenomegaly in the earlier series was infectious diseases and in the later series was hematologic disorder. The commonest diagnostic group in both series associated with massive splenomegaly was hematologic disorder. The relative number of patients with hematologic disorder in the later series (67%) was almost double that of the earlier series (34%). The relative number of patients with infectious diseases in the later series (8%) was decreased more than fivefold compared to the earlier series (43%). Massive splenomegaly as a percentage of total splenomegaly for all disease groups collectively occurred in 22% of all the patients, 31% for all the patients with a hematologic disorder, and was highest (36%) for the patients with primary splenic disease.

Table 2 shows all the hematologic diseases in diagnostic detail. All the patients with hematologic malignancy (the leukemias plus lymphoma and polycythemia vera) accounted for 83% (968 of 1,170 patients) of those with splenomegaly and 85% (309 of 365 patients) of those with massive splenomegaly. The relative frequency of acute leukemia in the later series more than doubled,

TABLE 2.—*Hematologic Diseases Associated With Splenomegaly and Massive Splenomegaly* *

	Total Splenomegaly, %		Subtotal With Massive Splenomegaly, %		
Diseases	1913 to 1936 (n = 214)	1937 to 1962 (n = 956)	1913 to 1936 (n = 81)	1937-1962) (n = 284)	% of Each Disease†
Lymphoma	24	4	23	5	37
CML	21	18	42	35	61
ALL/AML	16‡	36	10	20	17
Hemolytic anemia	13	11	14	7	23
Pernicious anemia	13	0.4	1	0	3
CLL	7	18	6	18	34
Polycythemia vera	4	9	2	7	23
Myelofibrosis	0	3	0	8	78
Other	2	0.4	0	0	0
Total	100	100	100	100	31

ALL = acute lymphoblastic leukemia, AML = acute myeloblastic leukemia, CLL = chronic lymphocytic leukemia, CML = chronic myelocytic leukemia

*Data are derived from patients from the earlier series (1913 to 1936) and the later series (1937 to 1962) at the University of California, San Francisco, School of Medicine. Other includes 4 patients with aplastic anemia, 3 with idiopathic thrombocytopenic purpura, and 1 with multiple myeloma.
†% of each disease indicates massive splenomegaly as a percentage of the total number of patients with splenomegaly.
‡Acute leukemia often was not differentiated in the earlier series.

TABLE 3.—*Infectious Diseases Associated With Splenomegaly and Massive Splenomegaly* *

	Total Splenomegaly, %		*Subtotal With Massive Splenomegaly, %*		
Diseases	*1913 to 1936 (n = 266)*	*1937 to 1962 (n = 119)*	*1913 to 1936 (n = 20)*	*1937 to 1962 (n = 9)*	*% of Each Disease*†
Malaria	27	8	65	33	20
Endocarditis	21	13	5	11	3
Tuberculosis	12	16	5	0	2
Respiratory	8	16	0	0	0
Acute and chronic inflammatory‡	9	13	0	11	3
Syphilis	6	8	20	33	27
Peritonitis or UTI	0/3	10/0	0	0	0
Sepsis	4	7	0	0	0
Typhoid fever	5	0	5	0	7
Brucellosis or amebiasis	2/2	0	0	0	0
Infectious mononucleosis	0	8	0	11	11
Coccidioidomycosis or cryptococcosis	0	2	0	0	0
Total	100	100	100	100	8

UTI = urinary tract infections

*Data are derived from patients from the earlier series (1913 to 1936) and the later series (1937 to 1962) at the University of California, San Francisco, School of Medicine.
†% of each disease indicates massive splenomegaly as a percentage of the total number of patients with splenomegaly.
‡Acute infections include bacterial meningitis, acute prostatitis, acute skin infection, and enteric fever. Chronic infections include chronic pyelonephritis, chronic skin infections, pelvic inflammatory disease, chronic foot infections, purulent pericarditis, and febrile reversible hepatosplenomegaly of childhood.

16% to 36%; of chronic leukemias, increased slightly from 28% to 36%; and of myelofibrosis, increased more than 30-fold from less than 0.1% to 3%. The relative frequency of lymphoma decreased 6-fold from 24% to 4%, and that of pernicious anemia decreased more than 30-fold from 13% to 0.4%. Massive splenomegaly as a percentage of total splenomegaly occurred in 31% of the entire group of patients with a hematologic disorder: 78% with myelofibrosis, 61% with chronic myelocytic leukemia (CML), 37% with lymphoma, 17% with acute leukemia, and 3% with pernicious anemia.

Table 3 shows the infectious diseases in diagnostic detail. The commonest disease for the combined series associated with both splenomegaly and massive splenomegaly was malaria, which occurred in 82 patients. The second most common disease associated with splenomegaly was endocarditis and, with massive splenomegaly, was syphilis. Massive splenomegaly as a percentage of total splenomegaly occurred in 8% of all patients with infectious diseases, 27% with syphilis, 20% with malaria, 3% with endocarditis, and 2% with tuberculosis.

Table 4 shows the hepatic diseases in diagnostic detail. Patients with a stated diagnosis of Banti's disease or syndrome were classified as having chronic liver disease. The commonest disease associated with both splenomegaly (129 patients) and massive splenomegaly was chronic liver disease. Alcoholic liver disease was associated with 28% of the splenomegaly but only 10% of the massive splenomegaly. Massive splenomegaly as a percentage of total splenomegaly occurred in 17% of all patients with hepatic disease, 25% of patients with chronic liver disease, and 7% of patients with alcoholic liver disease. The relative frequency of portal vein thrombosis in the earlier series compared with the later series increased fourfold from 2% to 8% and for biliary cirrhosis, increased (0% to 6%) even more. The increase in diagnostic frequency of portal vein thrombosis and biliary cirrhosis may reflect improved diagnostic understanding and techniques.

Table 4 also shows the inflammatory diseases in diagnostic detail. The commonest cause of splenomegaly was thyrotoxicosis (25 patients) and of massive splenomegaly was collagen disease. The relative frequency of Felty's syndrome in the earlier series compared with the later series increased almost fivefold, from 5% to 24%, that of thyrotoxicosis decreased more than twofold from 46% to 19%, and that of rheumatic disease decreased even more from 23% to 0%.

Table 4 also shows the primary splenic diseases in diagnostic detail. The commonest disease associated with splenomegaly was cystic diseases (10 patients). The commonest diseases associated with massive splenomegaly were cystic diseases in 70% and storage diseases in 75% of these patients.

Congestive heart failure (CHF) was associated with splenomegaly in 16 patients in the early series and 95 patients in the later one. In 64 patients (67%) from the later series, the enlarged spleen was not palpable but rather was discovered usually at autopsy and occasionally on radiologic study. Several causes for the heart disease were found: atherosclerosis in 38%, congenital heart disease in 31%, rheumatic heart disease in 18%, cor pulmonale in 8%, and other heart diseases in 5%. A palpable spleen was associated with congenital heart disease in

TABLE 4.—*Hepatic, Inflammatory, and Primary Splenic Diseases Associated With Splenomegaly and Massive Splenomegaly* *

	Total Splenomegaly, %		*Subtotal With Massive Splenomegaly, %*		
Diseases	1913 to 1936	1937 to 1962	1913 to 1936	1937 to 1962	*% of Each Disease*†
Hepatic	(n = 63)	(n = 157)	(n = 10)	(n = 29)	
Chronic liver	52	58	80	79	25
Alcoholic liver	35	24	20	7	7
Portal vein thrombosis	2	8	0	7	14
VH/hepatoma	11/0	3/2	0/0	0/0	0/0
Biliary cirrhosis	0	6	0	7	22
Total	100	100	100	100	17
Inflammatory	(n = 39)	(n = 37)	(n = 4)	(n = 2)	
Thyrotoxicosis	46	19	0	0	0
Collagen	21	22	50	50	19
Felty's syndrome	5	24	25	0	9
Rheumatic	23	0	0	0	0
Pancreatitis/IBD	3/0	5/8	0	0	0
Amyloidosis	3	11	25	50	40
Sarcoidosis	0	11	0	0	0
Total	100	100	100	100	8
Primary splenic	(n = 4)	(n = 24)	(n = 1)	(n = 9)	
Cystic	50	33	100	67	70
SVT	0	25	0	0	0
Infarcts	25	12	0	0	0
Storage disease	0	16	0	33	75
Metastases	25	12	0	0	0
Total	100	100	100	100	36

IBD = inflammatory bowel disease, SVT = splenic vein thrombosis, VH = viral hepatitis

*Data are derived from patients from the earlier series (1913 to 1936) and the later series (1937 to 1962) at the University of California, San Francisco, School of Medicine.
†% of Each Disease indicates massive splenomegaly as a percentage of the total number of patients with splenomegaly.

57% (17 of 30) of the patients, atherosclerosis in 26% (9 of 35), and rheumatic disease in 18% (3 of 17).

The spleen showed progressive enlargement during clinical observation in 88 patients: 9 in the earlier series and 79 in the later series. It showed a significant association ($P < .02$) with hematologic diseases (83%), especially the leukemias (Table 5). Progressive splenic enlargement also occurred in nonhematologic diseases: 5 had hepatic diseases, 4 had infectious diseases, 3 had primary splenic disease, and 3 had congestive or inflammatory disease.

Lymphadenopathy occurred in 40% of all the patients (Table 5) and was significantly associated ($P < .001$) with hematologic diseases. The individual lymphoproliferative diseases showed the highest incidence of patients with both lymphadenopathy and splenomegaly: lymphoma, 97% (96 of 99); chronic lymphoblastic leukemia (CLL), 80% (158 of 197); and acute lymphoblastic leukemia (ALL), 80% (151 of 188). Generalized lymphadenopathy occurred in 355 patients: 21 in the earlier series and 334 in the later one. Thus, generalized lymphadenopathy occurred in 43.0% (355 of 825) of the patients who had lymphadenopathy (Table 5) and was significantly associated ($P < .001$) with hematologic diseases. The lymphoproliferative diseases showed the highest incidence of generalized lymphadenopathy and splenomegaly: ALL, 57% (108 of 197); CLL, 55% (107 of 188); and lymphoma, 53% (52 of 99).

Percutaneous splenic puncture with a fine needle was performed in 16 patients of the combined series. A diagnosis was established in six of these patients: two had lymphoma, one had acute leukemia, one had CML, one had CLL, and one had subacute bacterial endocarditis. Most of the ten patients with normal findings were followed up with either a diagnostic splenectomy or an autopsy.

The 14 patients at UCSF with a friction rub heard over the spleen included 7 with infectious diseases (3 with endocarditis with splenic infarcts, 3 with disseminated tuberculosis, and 1 with infectious mononucleosis), 6 with hematologic malignancy (2 with CML, 2 with polycythemia vera, 1 with ALL, and 1 with CLL), and 1 patient with a large congenital splenic cyst. At the San Francisco General Hospital Medical Center, two patients had a splenic friction rub: one had disseminated tuberculosis, and the other had myelofibrosis with splenic infarct. Thus, 16 patients in all had a splenic friction rub: 10 with benign disease, and 6 with hematologic malignancy. Two patients had a splenic bruit: one had an arteriovenous malformation of the splenic blood vessels, and the other had CML and a simultaneous friction rub.

TABLE 5.—*Associations of Clinical and Laboratory Features With Diagnostic Groups of Splenomegaly (% of Patients)**

Diagnostic Group				
Features	*Hematologic*	*Infectious*	*Hepatic*	*Total*
Patients (N = 2,056), %	*57*	*19*	*11*	*100*
Clinical				
Hepatomegaly (n = 1,368)	.61	18	13	67
Lymphadenopathy (n = 825)	.78†	11	3	40
General lymphadenopathy (n = 355)	.88†	7	2	17
Massive splenomegaly (n = 452)	.81†	6	9	22
Progressive splenic enlargement (n = 88)	.83‡	5	6	4
Fever (n = 383)	.29	52†	5	19
Laboratory				
Cytosis (n = 1,037)	.85†	10	3	50
Cytopenia (n = 675)	.57	9	13	33
Abnormal liver function (n = 144)	.9	4	78†	7

*Data are derived from the total number of patients at the University of California, San Francisco, School of Medicine (UCSF) for earlier series and later series at UCSF combined. The diagnostic groups of congestive and inflammatory diseases and primary splenic or other diseases have been omitted for lack of any associations.
†$P<.001$.
‡$P<.02$.

Four patients had splenic calcification: one each with echinococcal cyst, tuberculosis, hematoma, and lymphoma. Four patients had splenomegaly that disappeared under observation: two disappeared spontaneously (with 1 infectious mononucleosis, and a 5-year-old child with splenomegaly of unknown origin), and two disappeared after treatment (1 child with surgical ligation of a patent ductus arteriosus, and 1 adult with vigorous diuresis of CHF).

Table 5 shows the statistical positive associations of the clinical and laboratory features of splenomegaly with three of the diagnostic groups. Hematologic diseases showed a significantly positive association ($P < .001$) with lymphadenopathy, generalized lymphadenopathy, massive splenomegaly, and cytosis and a significantly positive association with progressive splenic enlargement ($P < .02$). Infectious diseases showed a significantly positive association ($P < .001$) with fever. Hepatic diseases showed a significantly positive association ($P < .001$) with abnormal results on liver function tests.

Discussion

Infectious Diseases

Malaria. From about 1830 to 1930, malaria was endemic in the San Joaquin Valley of California.[7] California enacted the Mosquito Abatement District Act in 1915, which was associated within a decade of a tenfold decline in the reported incidence of malaria.[8] The many isolated outbreaks of malaria in California in the past 50 years have been imported by US civilians and military personnel and foreign-born civilians. They provided the gametocytemic source for the autochthonous transmission of malaria by female anopheline mosquitoes.[9] The chances for the transmission of imported malaria in California, however, generally are exceedingly small because of the low probability that infected mosquitoes will survive beyond the 12 to 14 days of maturation time required for the plasmodia.[9] After fever, splenomegaly is the commonest physical finding still being reported for malaria.[10] Most of the patients with malaria were referred to UCSF from the San Joaquin Valley, were febrile at the time of diagnosis (>60%), and had a peripheral blood smear positive for plasmodia (>80%).

Endocarditis. The bacteriologic findings of the 72 patients with endocarditis in the combined series was *Streptococcus viridans* in 61, β-hemolytic streptococcus in 9, nonhemolytic streptococcus in 1, and *Salmonella typhosa* in 1. These data are similar to most series reported from before the introduction of antibiotics: as many as 95% of the reported patients were infected by the less virulent *S viridans*.[11] The 9 patients in this series with the more virulent β-hemolytic streptococcus all had a rapidly fatal acute endocarditis.[12] The rest of the patients with endocarditis had a more long-term course, which was historically called "subacute."[13] Only one patient at UCSF had a *Salmonella* species as the infecting organism, as gram-negative organisms rarely caused endocarditis even before the antibiotic era.[14] One adult patient with nonhemolytic streptococcal endocarditis had luetic heart disease, an association rarely reported.[15] Of 22 patients with splenic infarct, 18 (82%) had an embolic origin: 17 had patients had endocarditis and 1 had atrial fibrillation. In the other four patients, splenic infarcts were hematologic in origin (18%): three had leukemia, and one had polycythemia vera. In a more recent large study of splenic infarction, only 38% of splenic infarcts were embolic in origin, but 14% of patients required a splenectomy for persistent symptoms or complications.[16]

No patients with splenic infarction at UCSF required a splenectomy, but 14 of the 22 patients died and an autopsy was performed.

Most series have reported a low incidence of endocarditis in children in the first decade of life (<1% of patients), yet an incidence of 10% (7 of 72) of endocarditis and splenomegaly was found to occur in early childhood at UCSF.[17] In fact, one patient was only 19 days old, whereas the youngest reported child found in the literature was said to be 10 months old.[18] Three of the five children in this series had endocarditis associated with congenital heart disease.[19] The disappearance of rheumatic heart disease in this country and the introduction of antibiotics have led to a marked decline in endocarditis as a cause of splenomegaly, except in patients with congenital heart disease or prosthetic heart valves or who are injection-drug users.[20]

Tuberculosis. Of 51 patients with tuberculosis and splenomegaly, 27 (53%) were adults and 24 (47%) were children. All the children and all but four of the adults showed evidence of disseminated tuberculosis. In a large study of miliary tuberculosis in children, the incidence of splenomegaly was 54% (57 of 94).[21] Lymphadenopathy and splenomegaly occurred in 22 (44%) of the patients with tuberculosis at UCSF. Three of the adult patients with hepatosplenomegaly had leukopenia, which may have represented tuberculous hepatitis with hypersplenism.[22]

Syphilis. Of 26 patients with syphilis and splenomegaly, 20 were adult. All 6 children had hepatosplenomegaly with leukopenia or thrombocytopenia, which may have represented hypersplenism of luetic hepatitis. All six children, ages newborn to 12 years, were said to have congenital syphilis. Splenomegaly is the most consistent physical sign of congenital syphilis.[23] Five adult patients at UCSF had luetic hepatitis, and one had gummas of the spleen. Syphilis of the central nervous system occurred in five adults: two had tabes dorsalis, and two others had deficits of cranial nerves. Lymphadenopathy occurred in 8 (47%) of the 17 luetic patients, 3 of whom had generalized lymphadenopathy. Splenomegaly has been reported in several luetic conditions: congenital syphilis,[23] syphilitic hepatitis,[24] secondary or mucocutaneous syphilis,[25] tertiary syphilis of the central nervous system, and gummas.[26]

Typhoid fever. Of 14 patients with typhoid fever and splenomegaly, 9 were adults. All (100%) these patients had fever, and none of them had diarrhea. Eight (67%) of the 12 patients in whom a WBC count was performed had typical leukopenia. Others have reported thrombocytopenia as being more common[27] and leukopenia not to be a helpful diagnostic marker.[28] Splenomegaly was the leading clinical sign after fever and bradycardia.[29] Typhoid fever has virtually disappeared as a cause of splenomegaly, as evidenced by its absence in the later series (1937-1962) at UCSF. A recent report from Johns Hopkins University Hospital, Baltimore, Maryland, confirmed this pronounced reduction in splenomegaly since Osler's report in 1900.[29–31] In keeping with other reports of typhoid fever, all the patients in this series had nonspecific and mild manifestations of disease and a uniformly favorable outcome.[31]

Brucellosis. Of the six patients with brucellosis and splenomegaly, three worked at UCSF. Two of these patients were animal handlers, and the third was a laboratory technician who worked with *Brucella* species. A fourth patient was a sausage maker, the fifth was a student at the University of California, Davis, School of Veterinary Medicine, and the sixth had been recently vaccinated for brucellosis.[32] *Brucella* species is so infectious that it can be acquired in the laboratory merely from sniffing bacteriologic cultures containing the organism.[33] In the past decade, brucellosis in California has shifted from an occupational disease to a food-borne infection acquired in Mexico or from imported Mexican foods such as unpasteurized dairy products.[34]

Hematologic Diseases

Leukemia. The commonest hematologic disease associated with massive splenomegaly for the series was CML. It is one of few diseases that frequently presents with massive splenomegaly (in this series, 61%), rivaled by malaria, myelofibrosis, and kala azar.[35] Massive splenomegaly was twofold less in patients with acute leukemia than in those with CML. Leukocytosis also occurred less frequently in patients with acute leukemia than in those with CML. Among patients with acute leukemia, thrombocytopenia occurred in 51% (193 of 378) and leukopenia in 11% (42 of 378). In marked contrast, no patient on presentation with CML had either thrombocytopenia or leukopenia. Not surprisingly, neither myelofibrosis nor agnogenic myeloid metaplasia was reported in the earlier series. This series predated the description in 1937 of the disease.[36] It often was not then diagnostically distinguishable from leukemia[37] and, in fact, was often called "pseudoleukemia."[38]

A major question is, why did the incidence of all of the leukemias increase fourfold in the later series at a time when the incidence of lymphoma declined sixfold compared with the earlier series at UCSF? Chemotherapy for the leukemias was discovered in the 1940s and flourished at UCSF in the 1950s.[39] A federally funded chemotherapy center was established at UCSF by 1950, and later the Cancer Research Institute was formed. The presence of these units may have led to a notable increase in referrals from the medical community for innovative treatment of leukemia. At the same time, the treatment of lymphoma at the nearby Stanford University Medical Center, in San Francisco (now in Palo Alto, was vigorously pursued. These referral patterns for the later series would have led to more patients with leukemia at UCSF and more patients with lymphoma at Stanford University Medical Center than in the earlier series.

Pernicious anemia. There were 31 patients with pernicious anemia and splenomegaly. The diagnosis was established in several ways: achylia gastrica on gastric aspiration in 10 patients, the presence of combined system disease on neurologic or postmortem examination of the spinal cord in 7 patients, megaloblastic changes on the peripheral blood smear or bone marrow examination in 7 patients, macrocytosis and cytopenia in 4 patients, low

serum vitamin B_{12} concentrations in 2 patients, and the presence of generalized vitiligo in 1 patient. Generalized vitiligo and pernicious anemia are both autoimmune diseases with frequent association.[40] Leukopenia or thrombocytopenia occurred in 25 (88%) patients with pernicious anemia. Although the cytopenias have markedly declined since the beginning of specific therapy with vitamin B_{12} in 1926,[41] splenomegaly and cytopenias are still being reported in patients with pernicious anemia.[42]

Generalized Lymphadenopathy

There was a high incidence of generalized lymphadenopathy in the later series (23%) compared with the earlier series at UCSF (3%). Generalized lymphadenopathy was significantly associated ($P < .001$) with hematologic diseases. This finding is consistent with the dramatic increase of hematologic disease as the basis for the marked increase of generalized lymphadenopathy in this series. Similarly, the tenfold absolute and fourfold relative increase in the incidence of progressive splenic enlargement in this series with its significant association ($P < .02$) with hematologic diseases could have the same explanation. The lymphadenopathy in the combined series was generalized in 44% (355 of 825 patients), whereas a previous report found it in less than a quarter of their patients.[43] Hematologic diseases accounted for 88% of the generalized lymphadenopathy in this study, whereas a previous study reported that infectious diseases was associated with a majority of their patients with generalized lymphadenopathy.[44]

Inflammatory and Congestive Diseases

Congestive heart failure. All 16 patients with CHF and splenomegaly in the earlier series had underlying rheumatic heart disease. It is unclear why the incidence of CHF and splenomegaly in the later series had a fourfold increased incidence (95 patients) relative to the earlier series at UCSF, for an total incidence of 5.4% (111 of 2,056 patients). One explanation is that most of the patients with CHF in the later series had splenomegaly detected only at autopsy. In a study of splenomegaly performed in the United States in the 1950s, CHF was still the leading cause of splenomegaly.[4] In a similar study from India for the same period as at UCSF, the spleen in CHF was palpable in 54 of 690 patients or 7.8%.[45] In that study, the highest incidence of CHF and palpable splenomegaly in a specific heart disease was endocarditis in 57% of the patients, whereas those with rheumatic heart disease had splenomegaly detected in only 11%. At autopsy, the incidence of mild splenomegaly (>200 grams) was 48% and of moderate splenomegaly (>300 grams) was 22%.[45] Other series of CHF of that same period from the United States also report a greater than 10% incidence of moderate splenomegaly (>300 grams) in patients with CHF.[46,47] As in this series, the incidence of palpable splenomegaly in patients with CHF was a small fraction of that found at autopsy.[46] Congestive heart failure is now rarely associated with splenomegaly in developed countries, perhaps because of the extensive use of oral diuretics, the better care of cardiac patients, and the growing disappearance of rheumatic heart disease with the availability of antibiotics.[48]

Thyrotoxicosis. Of 25 adult patients with thyrotoxicosis and splenomegaly, 16 were women. Exophthalmos occurred in 17 of the patients, and a diffuse goiter was found in 15 patients. Graves' disease was present in 15 (60%) of the patients. In a large study of Graves' disease from the same period, a 33% incidence (44 of 132 patients) of splenomegaly reported.[49] In contrast, in a study from the United States for 1983 to 1993, Graves' disease was found in only 1 of 170 patients with splenomegaly.[6] Lymphadenopathy and splenomegaly at UCSF occurred in 8 (44%) of the 18 patients in the earlier series. There was a sixfold reduction of splenomegaly in hyperthyroidism from the earlier series (18 of 621 patients, or 2.9%) at UCSF compared with the later one (7 of 1,435 patients, or 0.5%). Severe and long-standing hyperthyroidism in the earlier period was associated with splenomegaly as a part of generalized lymphoid hyperplasia.[49] Today, splenomegaly and hyperthyroidism rarely occur.[50] Yet, the persistence of splenomegaly and lymphadenopathy in thyrotoxicosis may represent its imperfect treatment due to the lack of specific therapy for the underlying autoimmune disease.[51]

Felty's syndrome with rheumatoid arthritis, splenomegaly, leukopenia, and chronic infection occurred in 11 patients. The 2 patients who had splenectomies improved clinically.[52]

Splenic Puncture

Percutaneous splenic puncture with a fine needle was performed in 16 patients; a diagnosis was established in 5 (38%) of the patients with hematologic disease and 1 patient with subacute bacterial endocarditis. Aspiration biopsies with fine needles provide only cytologic examination,[53] whereas histologic confirmation with a tissue-core biopsy may be required.[54] All 16 splenic punctures in this series were performed "blind," before the introduction of guidance by imaging. This blind approach may have contributed to the rupture of the splenic vessels in one patient, which necessitated an emergency splenectomy.

Splenic Friction Rub

Sixteen patients had splenic friction rubs: eight with infectious diseases, six with hematologic malignancy, one with myelofibrosis, and one with primary splenic disease. At least three of the six patients with a hematologic disease and splenic friction rub had splenic infarcts. Osler noted in the 1906 edition of his textbook that on several occasions he had heard a peritoneal friction rub in patients with splenic infarcts,[55] an observation later confirmed by others.[56,57] One patient reported with a splenic abscess had a pleural friction rub that probably was related to the associated pleural disease.[58] A standard textbook on clinical diagnosis stated that splenic friction rubs were heard in patients with splenic infarction, neoplasia, and infections.[59] Splenic friction rubs were said to occur in patients with perisplenitis and with infarcts of the spleen of any source.[60] In that same report, two patients presented with splenic friction rubs: one had

chronic leukemia, and the other had subacute bacterial endocarditis.[60] Splenic friction rubs had been reported in patients with splenic infarcts and with chronic leukemia.[61]

Contrarily, most hepatic friction rubs are associated with malignancy, usually solid tumors that are metastatic to the liver.[62] Systolic arterial murmurs or bruits over the liver or adjacent chest were found in hepatomas because they are very vascular tumors.[63]

Vascular murmurs or splenic bruits were heard over greatly enlarged spleens in patients with benign diseases or with hematologic malignancy[64] and were said to result from increased blood flow of the greatly enlarged organ.[56] The one patient in this series with an arteriovenous malformation of the splenic blood vessels had a splenic bruit. Thus, the sounds heard in patients at UCSF over enlarged spleens of benign diseases and several hematologic cancers were all said to be friction rubs that should have been synchronous with respiration, whereas the sounds (bruits) reported over greatly enlarged spleens were demonstrated by phonocardiography to be vascular murmurs synchronous with the pulse.[56]

Acknowledgment

I am grateful to Lloyd H. Smith Jr, MD, formerly associate editor of THE WESTERN JOURNAL OF MEDICINE, for his critical review of the manuscript and his many helpful suggestions.

REFERENCES

1. Osler W. Discussion on splenic enlargements other than leukaemic. BMJ 1908; 2:1151–1158

2. De Cock KM, Hodgen AN, Lucas SB, et al. Chronic splenomegaly in Nairobi, Kenya. I. Epidemiology, malarial antibody and immunoglobulin levels. Trans R Soc Trop Med Hyg 1987; 81:100–106

3. Lipp WF, Eckstein EH, Aaron AH. The clinical significance of the palpable spleen. Gastroenterology 1944; 3:287–291

4. Schloesser LL. The diagnostic significance of splenomegaly. Am J Med Sci 1963; 245:84–90

5. Letoquart JP, La Gamma A, Kunin N, Grosbois B, Mambrini A, Leblay R. Splenectomy for splenomegaly exceeding 1000 grams: analysis of 47 patients. Br J Surg 1993; 80:334–335

6. O'Reilly RA. Splenomegaly at a United States county hospital: diagnostic evaluation of 170 patients. Am J Med Sci 1996; 312:160–165

7. Gray HF, Fontaine RE. A history of malaria in California. Proceedings of the 25th Annual Conference of the California Mosquito Control Association; January 21–23, 1957; San Jose, Calif. Oakland (Calif): Abbey Press, 1957; pp 18–39

8. Breslow L. Public health report. West J Med 1967; 106:496–497

9. Zucker JR. Changing patterns of autochthonous malaria transmission in the United States: a review of recent outbreaks. Emerg Infect Dis 1996; 2:37–43

10. Svenson JE, MacLean JD, Gyorkos TW, Keystone J. Imported malaria: clinical presentation and examination of symptomatic travelers. Arch Intern Med 1995; 155:861–868

11. Schottmüller H. Die Artunterscheidung der für den Menschen pathogenen Streptokokken durch Blutagar. München Med Wochenschr 1903; 50:849–853, 909–912

12. Savage D, Brown J. Endocarditis due to group A streptococcus. Am J Med Sci 1981; 282:98–103

13. Libman E, Celler HL. The etiology of subacute infective endocarditis. Am J Med Sci 1910; 140:516–527

14. Schneider PJ, Nernoff J III, Gold JA. Acute *Salmonella* endocarditis: report of a case and review. Arch Intern Med 1967; 120:478–482

15. Briggs LH. Bacterial endocarditis as a sequel to syphilitic valve defect. Am J Med Sci 1922; 164:275–281

16. Jaroch MT, Broughan TA, Hermann RE. The natural history of splenic infarction. Surgery 1986; 100:743–749

17. Lawson GM, Palmer RS. Occurrence of subacute bacterial endocarditis in childhood. N Engl J Med 1928; 199:1205–1207

18. Aubert A, Lerche C. Subacute bacterial endocarditis in a child, ten months old, successfully treated with streptomycin. Am Heart J 1950; 39:141–143

19. Abbott ME. On the incidence of bacterial inflammatory processes in cardio-vascular defects and on malformed semilunar cusps. Ann Clin Med 1925-26;4:189–218

20. Dressler FA, Roberts WC. Infective endocarditis in opiate addicts: analysis of 80 cases studied at necropsy. Am J Cardiol 1989; 63:1240–1257

21. Hussey G, Chisholm T, Kibel M. Miliary tuberculosis in children: a review of 94 cases. Pediatr Infect Dis J 1991; 10:832–836

22. Essop AR, Posen JA, Hodkinson JH, Segal I. Tuberculosis hepatitis: a clinical review of 96 cases. Q J Med 1984; 53:465–477

23. Koh MT, Lim CT. Early congenital syphilis: experience with 13 consecutive cases seen at the University Hospital, Kuala Lumpur. Singapore Med J 1991; 32:230–232

24. Fehér J, Somogyi T, Timmer M, Józsa L. Early syphilitic hepatitis. Lancet 1975; 2:896–899

25. Archambeaud-Mouveroux F, Morand P, Bernard P, et al. Liver involvement in secondary syphilis [French]. Gastroenterol Clin Biol 1987; 11:93–95

26. Pérez CM, León A, Oddó D, et al. Isolated gummatous splenitis. Clin Infect Dis 1995; 21:228–229

27. Hustinx WNM, Speelman YNEP. Typhoid and paratyphoid fever in two university hospitals: 1984–1990 [Dutch]. Ned Tijdschr Geneeskd 1993; 137:291–294

28. Yew FS, Chew SK, Goh KT, Monteiro EHA, Lim YS. Typhoid fever in Singapore: a review of 370 cases. J Trop Med Hyg 1991; 94:352–357

29. Zenilman JM. Grand Rounds at The Johns Hopkins Hospital: typhoid fever. JAMA 1997; 278:847–850

30. Osler W. Analysis and general summary of the cases [of typhoid fever] from 1889–1899. Johns Hopkins Hosp Rep 1900; 8:421–422

31. Klotz SA, Jorgensen JH, Buckwold FJ, Craven PC. Typhoid fever: an epidemic with remarkably few clinical signs and symptoms. Arch Intern Med 1984; 144:533–537

32. Crosby E, Llosa L, Quesada MM, Carrillo PC, Gotuzzo E. Hematologic changes in brucellosis. J Infect Dis 1984; 150:419–424

33. Grammont-Cupillard M, Berthet-Badetti L, Dellamonica P. Brucellosis from sniffing bacteriological cultures. Lancet 1996; 348:1733–1734

34. Applebaum GD, Mathisen G. Spinal brucellosis in a southern California resident. West J Med 1997; 166:61–65

35. Jandl JH. Blood: textbook of hematology, 2nd ed. Boston (Mass): Little, Brown; 1996, p 908

36. Jackson H Jr, Parker F Jr, Lemon HM. Agnogenic myeloid metaplasia of the spleen: a syndrome simulating other more definite hematologic disorders. N Engl J Med 1940; 222:985–994

37. Block M, Jacobson LO. Myeloid metaplasia. JAMA 1950; 143:1390–1396

38. Arneth P: Myeloisch-pseudoleukämische Reaktion ('aleukämische Myelose') und Milzexstirpation bei qualitativer Betrachtung. Wien Med Wochenschr 1932; 50:1544–1546

39. Farber S. Diamond LK, Mercer RD, Sylvester RF Jr, Wolff JA. Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid (aminopterin). N Engl J Med 1948; 238:787–793

40. Held JL, Kohn SR. Vitiligo and pernicious anemia presenting as congestive heart failure. Cutis 1990; 46:268–270

41. Davidson S. Clinical picture of pernicious anaemia prior to introduction of liver therapy in 1926 and in Edinburgh subsequent to 1944. BMJ 1957; 1:241–243

42. Pruthi RK, Tefferi A, Petitt RM. Reversible marked splenomegaly in pernicious anemia. Ann Intern Med 1993; 119:1053

43. Allhiser JN, McKnight TA, Shank JC. Lymphadenopathy in a family practice. J Fam Pract 1981; 12:27–32

44. Libman H. Clinical reviews: generalized lymphadenopathy. J Gen Intern Med 1987; 2:48–58

45. Wahi PN, Mathur KS. Splenomegaly in congestive heart failure: a study of 690 cases with review of literature. Indian Heart J 1949; 1:230–239

46. Fowler NO Jr. Splenomegaly in congestive heart failure. Ann Intern Med 1947; 27:733–737

47. Arnett JH. Splenic and hepatic enlargement in endocarditis: a study of two hundred and eight-six autopsy findings. Am J Med Sci 1922; 163:590–594

48. Firkin BG. As time goes by: reflections on 40 years of academic medicine and biomedical research. Med J Aust 1995; 163:604–606

49. Baldridge CW, Peterson FR. Splenic enlargement in hyperthyroidism. JAMA 1927; 88:1701–1702

50. Marynick SP. Splenomegaly in thyrotoxicosis. JAMA 1982; 247:2782

51. Eastman CJ. Graves' disease 150 years on [Editorial]. Med J Aust 1996; 165:467–468

52. Rosenstein ED, Kramer N. Felty's and pseudo-Felty's syndromes. Semin Arthritis Rheum 1991; 21:129–142

53. Lishner M, Lang R, Hamlet Y, et al. Fine needle aspiration biopsy in patients with diffusely enlarged spleens. Acta Cytol 1996; 40:196–198

54. Cavanna L, Civardi G, Fornari F, et al. Ultrasonically guided percutaneous splenic tissue core biopsy in patients with malignant lymphomas. Cancer 1992; 69:2932–2936

55. Osler W. The principles and practice of medicine, 6th ed. New York (NY): D Appleton; 1906, p 761

56. Björkman SE. On the occurrence of a vascular murmur over greatly enlarged spleens. J Intern Med 1953; 145:79–83

57. Eichner ER. Splenomegaly, In: Taylor RB, editor. Difficult diagnosis. Philadelphia (Pa): WB Saunders; 1985, pp 492–497

58. Freund R, Pichl J, Heyder N, Rödl W, Riemann JF. Splenic abscess—clinical symptoms and diagnostic possibilities. Am J Gastroenterol 1982; 77:35–38

59. Judge RD, Zuidema GD, Fitzgerald FT. Clinical diagnosis: a physiologic approach, 4th ed. Boston (Mass): Little, Brown; 1982, p 298

60. Babey AM. Friction rubs in the abdomen. Brooklyn Hosp J 1948; 6:15–18

61. Lindeboom GA. Friction rub sounds in the abdomen [Dutch]. Ned Tijdschr Geneeskd 1964; 108:2113–2117

62. Fenster LF, Klatskin G. Manifestations of metastatic tumors of the liver: a study of eighty-one patients subjected to needle biopsy. Am J Med 1961; 31:238–248

63. Clain D, Wartnaby K, Sherlock S. Abdominal arterial murmurs in liver disease. Lancet 1966; 2:516–519

64. Jain SR, Kathpal GS, Sepaha GC, Raman R. Splenic bruit. J Assoc Physicians India 1969; 17:537–541

Articles

Splenomegaly in 2,505 Patients at a Large University Medical Center From 1913 to 1995

1963 to 1995: 449 Patients

ROBERT A. O'REILLY, MD, *San Francisco, California*

Splenomegaly was studied retrospectively at the University of California, San Francisco (UCSF), School of Medicine in 301 patients from 1963 to 1995 and compared with the UCSF service of the San Francisco General Hospital Medical Center (SFGH) in 148 patients from 1979 to 1994. The combined 449 patients were classified into several diagnostic groups and were studied by means of several clinical and laboratory associations. Hepatic disease in the percentage of patients at UCSF (with those at SFGH given in parentheses) was associated with splenomegaly in 29% (41%), hematologic disease, 32% (16%); infectious diseases, 16% (36%); congestive or inflammatory diseases, 10% (4%); primary splenic disease, 6% (1%); other, 5% (1%); and cause unknown, 2% (1%). Massive splenomegaly occurred in 27% of the patients of the combined series, particularly in patients with hematologic diseases. The acquired immunodeficiency syndrome (AIDS) occurred in more than half of the patients with infectious diseases at SFGH and was four times more frequent than in the patients at UCSF. The commonest diseases associated with splenomegaly were hematologic (lymphoma), hepatic (chronic liver disease), infectious diseases (AIDS and endocarditis), congestive (congestive heart failure), primary splenic (splenic vein thrombosis), and other (malignancy not metastatic to the spleen). In 11 patients with AIDS and massive splenomegaly, *Mycobacterium avium* complex occurred in 8 (73%). Splenectomy was performed in 117 patients (26%), primarily for hematologic amelioration. I conclude that for splenomegaly of unknown origin, the invasive procedure of choice for patients with hematologic associations may be a bone marrow biopsy; for hepatic associations, a liver biopsy; and for infectious disease associations, a lymph node biopsy, before any consideration of a diagnostic splenectomy.

(O'Reilly RA. Splenomegaly in 2,505 patients at a large university medical center from 1913 to 1995. 1963 to 1995: 449 patients. West J Med 1998; 169:88–97)

Splenomegaly presents a diagnostic challenge because nearly always it is due to another primary disorder.[1] The only analyses from a developed country on splenomegaly in general were two office-based studies performed decades ago in which no diagnosis was established in more than 25% of the patients.[2,3] Only a single study of hospital-based patients in the United States has been reported.[4] Now, a second municipal hospital has been studied, San Francisco General Hospital Medical Center (SFGH), which has been compared with and contrasted to a university medical center at the University of California, San Francisco (UCSF), School of Medicine for about the same period. Infections with the human immunodeficiency virus (HIV) and with diseases related to the acquired immunodeficiency syndrome (AIDS) are prevalent in the young male homosexual community of northern California. The centering of AIDS patients at the SFGH and to a lesser extent at UCSF allowed the assessment of the development of AIDS on the diagnostic evaluation of splenomegaly and massive splenomegaly.

Patients and Methods

Patient Demographics

All hospital records at SFGH for patients of any age diagnostically coded as splenomegaly from 1979 through 1994 were reviewed retrospectively. Splenomegaly was defined as an enlarged spleen determined by one of the following: palpable by at least two clinicians or noted on two written observations, greater than 12 cm in length on radiologic imaging study, or more than 250 grams wet weight on an

From the Departments of Medicine, University of California, San Francisco, School of Medicine; Stanford University Medical Center, Palo Alto; and the Santa Clara Valley Medical Center, San Jose, California.

Reprint requests to Robert A. O'Reilly, MD, 751 S Bascom Ave, San Jose, CA 95128.

ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CLL = chronic lymphocytic leukemia
CML = chronic myelocytic leukemia
HIV = human immunodeficiency virus
ITP = idiopathic thrombocytopenic purpura
PVT = portal vein thrombosis
SFGH = San Francisco General Hospital Medical Center
SVT = splenic vein thrombosis
UCSF = University of California, San Francisco

excised spleen from a surgical procedure or autopsy. A total of 331 patients were coded as having splenomegaly at UCSF for the years 1963 to 1995; 30 medical records (9%) could not be found. Therefore, the study was based on the remaining 301 patients. A total of 193 patients at SFGH were coded as having splenomegaly; 45 medical records (23%) could not be found. Therefore, the study was based on the remaining 148 patients. The incidence of splenomegaly for these years at UCSF was 301 patients from about 90,000 admissions, or 0.3%.

Clinical and Laboratory Features

The detailed criteria for the analysis of the clinical and laboratory features of the patients are all listed in the first part of this study.[5]

Results

Patients ranged in age from newborn to 88 years, with a median age of 45 years at UCSF and 41 years at SFGH. Nine percent of the patients were younger than 18 years, and 3% were older than 80 years. Of the 148 patients at SFGH, 121 (82%) were male; of the 301 patients at UCSF, 160 (53%) were male. The higher frequency of male patients and the younger age at SFGH probably reflected the young gay male population of San Francisco. More than 98% of the patients were admitted to a hospital at some time, which allowed the assignment to a diagnostic group of all but 8 patients (2%) for the combined series of patients at UCSF and SFGH. Splenomegaly was detected by physical examination alone in 288 (64%) of 449 patients and by additional objective methods in 161 patients (36%): physical examination and abdominal imaging in 131 patients (29%), imaging only in 22 patients (5%), and surgical procedure only in 8 patients (2%). Thus, abdominal imaging was used in this study to detect splenomegaly in 153 (34%) of 449 patients.

Table 1 shows all the patients at UCSF and SFGH with splenomegaly and massive splenomegaly by diagnostic group. The commonest disease group at UCSF associated with splenomegaly was hematologic disease, closely followed by hepatic disease. Contrarily, the commonest disease group at SFGH associated with splenomegaly was hepatic disease, closely followed by infectious disease. At UCSF, half the patients in the hematologic group had massive splenomegaly. The commonest disease groups at SFGH associated with massive splenomegaly were hepatic and hematologic diseases equally. Massive splenomegaly as a percentage of the total number of patients with splenomegaly for the combined series for all disease groups collectively occurred in 27%. The contribution from UCSF to the combined series was 67% (301 of 449 patients) of the splenomegaly and 75% (91 of 121 patients) of the massive splenomegaly. The absolute number of patients at UCSF with splenomegaly was 301 during 32 years, or about 9 per year. Similarly, the absolute number of patients at SFGH with splenomegaly was 148 during 15 years, or about 10 per year. For the first series at UCSF from 1913 to 1936, splenomegaly was found in 621 patients, or about 27 per year. For the second series at UCSF from 1937 to 1962, it occurred in 1,435 patients, or 57 per year.

TABLE 1.—*All Causes of Splenomegaly and Massive Splenomegaly by Diagnostic Group**

Diagnostic Group	*Total Splenomegaly, %*		*Subtotal With Massive Splenomegaly, %*		
	UCSF (n = 301)	*SFGH (n = 148)*	*UCSF (n = 91)*	*SFGH (n = 30)*	*% of Each Diagnostic Group†*
Hepatic	29	41	21	33	20
Hematologic	32	16	53	33	48
Infectious	16	36	9	30	18
Congestive or inflammatory	10	4	2	0	6
Primary splenic	6	1	9	3	45
Other	5	1	7	0	38
Cause unknown	2	1	0	0	0
Total	100	100	100	100	27

SFGH = San Francisco General Hospital Medical Center, UCSF = University of California, San Francisco, School of Medicine

*Data are given as the percentage of patients at UCSF and SFGH, 1963 to 1995. Other refers to malignant disease not metastatic to the spleen, storage diseases, and miscellaneous.
†% of Each Diagnostic Group indicates massive splenomegaly as a percentage of the total number of patients with splenomegaly.

TABLE 2.—*Hepatic, Congestive or Inflammatory, Primary Splenic, and Other Diseases Associated With Splenomegaly and Massive Splenomegaly**

	Total Splenomegaly, %		*Subtotal With Massive Splenomegaly, %*		
Diagnostic Group	*UCSF*	*SFGH*	*UCSF*	*SFGH*	*% of Each Disease†*
Hepatic	(n = 87)	(n = 61)	(n = 19)	(n = 10)	
Chronic	49	38	53	50	23
Alcoholic	33	55	32	40	16
Viral hepatitis	9	3	0	10	10
PVT	7	2	16	0	43
Hepatoma	2	2	0	0	0
Total	100	100	100	100	20
Congestive or inflammatory	(n = 31)	(n = 6)	(n = 2)	(n = 0)	
CHF	48	33	0	0	0
Collagen or rheumatic	36	17	100	0	17
Other than‡	13	0	0	0	0
Pancreatitis	3	50	0	0	0
Total	100	100	100	100	5
Primary splenic	(n = 18)	(n = 2)	(n = 4)	(n = 1)	
SVT	44	0	50	0	25
Infarct or hematoma	16	100	0	100	20
Miscellaneous§	29	0	50	0	40
Abscess	11	0	0	0	0
Total	100	100	100	100	25
Other	(n = 22)	(n = 2)	(n = 6)	(n = 0)	
Malignancy‖	50	50	0	0	0
Storage disease	17	0	50	0	75
Cause unknown	17	50	0	0	0
Also#	16	0	50	0	75
Total	100	100	100	100	25

CHF = congestive heart failure, PVT = portal vein thrombosis, SFGH = San Francisco General Hospital Medical Center, SVT = splenic vein thrombosis, UCSF = University of California, San Francisco, School of Medicine

*Data are given as the percentage of patients at UCSF and SFGH for 1963 to 1995.

†% of Each Disease indicates massive splenomegaly as a percentage of the total number of patients with splenomegaly.

‡Other than indicates psoriasis, inflammatory bowel disease, amyloidosis, and Graves' disease (1 patient each).

§Miscellaneous indicates a congenital splenic cyst, splenic lymphopenia, lymphatic hyperplasia, uterine carcinoma metastatic to the spleen, and arteriovenous malformation of the splenic blood vessels (1 patient each).

‖Malignancy indicates cancer *not* metastatic to the spleen

#Also indicates histiocytosis X, splenic lymphopenia, hemophagocytic syndrome, and craniofacial syndrome

Table 2 shows that the commonest hepatic disease associated with splenomegaly at UCSF was chronic liver disease and at SFGH was alcoholic liver disease. The commonest disease with massive splenomegaly at both UCSF and SFGH was chronic liver disease. Portal vein thrombosis (PVT) occurred in seven patients, six of whom were at UCSF. Similarly, viral hepatitis occurred in ten patients, eight of whom were at UCSF. Contrarily, pancreatitis occurred in four patients, three of whom were at SFGH. In the congestive or inflammatory diseases group, the commonest disease associated with splenomegaly in the combined UCSF-SFGH series was congestive heart failure (45%), followed by collagen-rheumatic diseases (30%). In the primary splenic group, all eight patients with splenic vein thrombosis (SVT) were at UCSF. Three of four patients with storage disease had massive splenomegaly.

Table 3 shows that lymphoma was the commonest hematologic disease associated with both splenomegaly and massive splenomegaly. The chronic leukemias, chronic lymphocytic leukemia (CLL) and chronic myelocytic leukemia (CML), were twice as common as the acute leukemias for splenomegaly and six times more common for massive splenomegaly. In the combined SFGH-UCSF series, the commonest disease of erythrocytes associated with splenomegaly was hemoglobinopathy, and with massive splenomegaly was myelofibrosis. Hemoglobinopathy was found in 13 patients: 6 with thalassemia, 5 with hemoglobin SC disease, 1 with hemoglobin SS disease, and 1 with β^{o}-thalassemia–hemoglobin E. The highest incidence of massive splenomegaly for a disease was myelofibrosis (100%). Massive splenomegaly occurred in 58 (47%) of 124 patients of all the patients with hematologic disease.

TABLE 3.—*Hematologic Diseases Associated With Splenomegaly and Massive Splenomegaly**

	Total Splenomegaly, %		*Subtotal With Massive Splenomegaly, %*		
Diseases	*UCSF (n = 100)*	*SFGH (n = 24)*	*UCSF (n = 48)*	*SFGH (n = 10)*	*% of Each Disease*†
Lymphoma	29	25	33	40	57
CML	16	8	11	20	39
Hemoglobinopathy	7	25	6	20	38
Myelofibrosis	10	9	21	20	100
Acute leukemia	8	8	4	0	20
CLL	10	0	11	0	50
Hemolytic anemia	8	4	6	0	33
Preleukemia	3	0	3	0	33
Polycythemia vera	6	0	4	0	33
Other‡	2	13	0	0	0
MDS or MPD	2	8	2	0	25
Total	100	100	100	100	47

CLL = chronic lymphocytic leukemia, CML = chronic myelocytic leukemia, MDS = myelodysplastic syndrome, MPD = myeloproliferative disease, SFGH = San Francisco General Hospital Medical Center, UCSF = University of California, San Francisco, School of Medicine

*Data are given as the percentage of patients at UCSF and SFGH.
†% of Each Disease indicates massive splenomegaly as a percentage of the total number of patients with splenomegaly.
‡Other indicates hypereosinophilic syndrome (2 patients), malignant histiocytosis (1 patient), Diamond-Blackfan syndrome (1 patient), and idiopathic thrombocytopenic purpura (1 patient).

Table 4 shows the infectious diseases in diagnostic detail. At SFGH, AIDS was much more frequently associated with both splenomegaly and massive splenomegaly than at UCSF. The commonest infectious disease associated with massive splenomegaly was *Mycobacterium avium* complex, found in 7 (47%) of 15 patients. The commonest non-AIDS–related disease associated with splenomegaly was endocarditis, which was usually found (>90%) in injection drug users.

Two patients at SFGH had a splenic friction rub, and one patient at UCSF had a splenic bruit. One patient with a friction rub had myelofibrosis with a splenic infarct and the other patient had disseminated tuberculosis. The patient with the splenic bruit had an arteriovenous malformation of the splenic blood vessels.

Table 5 shows progressive enlargement of the spleen during clinical observation for six hospital series of splenomegaly, three from UCSF and one each from SFGH, Santa Clara Valley Medical Center, San Jose,[4] and the Stanford University Medical Center, Palo Alto, California (unpublished observations February 1994). The overall incidence was 117 of 2,822 patients, or 4.1%. Hematologic diseases accounted for most of these patients (98 [84%] of 117 patients), especially hematologic malignancy. The other 19 patients were in the following disease groups: 6 with infectious disease (4 with tuberculosis, 1 with subacute bacterial endocarditis, and 1 with schistosomiasis), 5 with hepatic disease (2 with chronic liver disease, 1 with biliary cirrhosis, 1 with alcoholic liver disease, and 1 with acute hepatitis), 5 with primary splenic disease or other (2 with cystic disease, and 1 patient each with splenic hemangioma, metastases to the abdominal viscera, and histiocytosis X), and 3 with congestive or inflammatory diseases (2 with Felty's syndrome and 1 with congestive heart failure). The highest incidence of progressive splenic enlargement (>5%) occurred in those series with a high incidence of hematologic diseases: patients at UCSF from 1937 to 1962, those at UCSF from 1963 to 1995, and patients at Stanford University Medical Center.

Table 6 shows the patients who had splenectomy for all the series at UCSF plus those at SFGH. The incidence of splenectomy was 7% (170 of 2,505 patients). The disease group with the highest incidence of splenectomy was hematologic disease (110 patients [65%]), followed by hepatic disease (34 patients [20%]). The commonest indication for splenectomy was amelioration or a curative operation, particularly for hematologic diseases like hemolytic anemias. Splenectomy for hypersplenism occurred in 37 patients (22%), particularly patients with hepatic and hematologic diseases. Splenectomy was performed in 20 patients (12%) for diagnosis, generally for splenomegaly of unknown cause. A diagnosis was established in all 20 of these patients: 6 with hepatic disease (4 with PVT, 1 with chronic liver disease, and 1 with alcoholic liver disease); 5 with hematologic disease (2 with CML, 1 with CLL, 1 with lymphoma, and 1 with myelofibrosis); 5 with infectious disease (2 with tuberculosis, 1 with endocarditis, 1 with syphilis, and 1 with respiratory tract disease); and 1 patient each with sarcoidosis, Letterer-Siwe disease, thyrotoxicosis, and splenic cyst. Thirty patients (18%) had a splenectomy associated with massive splenomegaly. Most of these patients had hematologic diseases, especially 13 with hereditary spherocytosis.

TABLE 4.—*Infectious Diseases Associated With Splenomegaly and Massive Splenomegaly**

	Splenomegaly, %		*Massive Splenomegaly, %*		
Disease	*UCSF (n = 48)*	*SFGH (n = 53)*	*UCSF (n = 8)*	*SFGH (n = 9)*	*% of Each Disease*† 17*
AIDS Related	(n = 8)	(n = 30)	(n = 3)	(n = 7)	
AIDS only	75	47	33	29	15
Mycobacterium avium complex	25	43	67	71	47
Opportunistic‡	0	10	0	0	0
Total	100	100	100	100	26
Non-AIDS-Related	(n = 40)	(n = 23)	(n = 5)	(n = 2)	
Endocarditis	12	43	20	0	7
Acute§	23	9	0	50	9
Chronic‖	10	26	0	0	0
Infectious mono	10	0	0	0	0
Injection drug use	10	0	0	0	0
Hypoglobulinemia	10	0	0	0	0
FUO	9	0	20	0	25
Malaria	8	0	20	0	33
Tuberculosis	5	4	20	0	33
Schistosomiasis	3	9	20	50	67
Sarcoidosis	0	9	0	0	0
Total	100	100	100	100	11

AIDS = acquired immunodeficiency syndrome, FUO = fever of unknown origin, mono = mononucleosis, SFGH = San Francisco General Hospital Medical Center, UCSF = University of California, San Francisco, School of Medicine

*Data are given as the percentage of patients at UCSF and SFGH for 1963 to 1995.
†% of each disease indicates massive splenomegaly as a percentage of the total number of patients with splenomegaly.
‡Opportunistic refers to disseminated histoplasmosis, cryptococcosis, or cytomegalovirus.
§Acute refers to conditions such as sepsis, viral syndromes in children, aspiration pneumonia, urosepsis, and fever and thrombocytopenia in a child.
‖Chronic refers to conditions such as abscesses, recurrent skin infections, recurrent respiratory tract infections, urinary tract infections, bronchiolitis, or chronic infections of several organs.

Discussion

Lymphoma

Lymphoma was again the leading hematologic cause of splenomegaly in this series at UCSF (29%, 1963-1995), as it was in the earliest series (24%, 1913-1936) at UCSF. The patients with lymphoma and splenomegaly in all three series had a high incidence of lymphadenopathy: 98% (50 of 51), 97% (37 of 38), and 68% (20 of 29), respectively. The percentage of these patients with generalized lymphadenopathy was 11% (6 of 51), 55% (21 of 38), and 7% (2 of 29), respectively. Massive splenomegaly occurred in 37% (19 of 57), 39% (15 of 39), and 59% (17 of 29), respectively. Chylous ascites occurred in six patients in all the series at UCSF: two with lymphoma in the earliest series (1 also with chylous hydrothorax), two with lymphoma in the next series, and one with lymphoma in the third series (1963-1995), and 1 patient with CLL in the second series. Chylous ascites is usually associated with extensive involvement of the retroperitoneal lymph nodes by a slow-growing lymphoproliferative malignant disease such as lymphoma and CLL.[6]

Progressive Splenic Enlargement

Splenomegaly is a nonspecific finding caused by so many diseases that comprehensive lists are clinically useless.[7] Yet, splenomegaly of any size warrants evaluation as to its cause. *Progressive* splenic enlargement observed clinically or radiologically demands diagnostic study because these patients usually have a hematologic cancer.[8] In fact, 84% of the patients at UCSF (Table 5) had hematologic cancers. Past reports on progressive splenic enlargement in hematologic malignancy include chronic myeloproliferative syndromes,[9] particularly patients in whom thrombosis of the major abdominal veins developed,[10] and evolving CLL dominated by hypersplenism.[11] In AIDS patients with disseminated *M avium* complex[12] or disseminated histoplasmosis,[13] rapidly progressive splenomegaly developed. Even patients with inflammatory diseases like progressive systemic sclerosis had the abrupt development of massive splenomegaly and Felty's syndrome.[14] Splenic cysts often enlarged rapidly and caused acute splenomegaly within a few weeks, as occurred in one of the patients of the second series at UCSF.[15] In Gaucher's disease, even partial splenectomy accelerated the disease and resulted in the recurrence of splenomegaly.[16] In all, progressive splenic enlargement for nonhematologic diseases occurred in 19 patients, 18 of whom had benign disease. Thus, progressive splenic enlargement in hematologic patients was usually malignant and in nonhematologic patients was usually benign, albeit often of serious consequence.

TABLE 5.—*Progressive Splenic Enlargement in Six Series of Splenomegaly**

Series	Patients, No.	Hematologic	Infectious Diseases	Hepatic	Primary Splenic or Other	Congestive-Inflammatory	Total Series	% of Series
UCSF								
1913 to 1936	621	3	3	3	0	0	9	1.4
1937 to 1962	1,435	70	1	2	4	2	79	5.5
1963 to 1995	301	14	0	0	1	1	16	5.3
SFGH								
1979 to 1994	148	2	1	0	0	0	3	2.0
Stanford								
1986 to 1994	147	8	0	0	0	0	8	5.4
Santa Clara VMC	170	1	1	0	0	0	2	1.2
Total	2,822	98	6	5	5	3	117	4.1

SFGH = San Francisco General Hospital Medical Center, UCSF = University of California, San Francisco

*Data are the number of patients at UCSF. Stanford refers to Stanford University Medical Center, Palo Alto, California (unpublished data). Santa Clara VMC refers to Valley Medical Center, San Jose, California.

Splenic Cysts

Of the ten patients at UCSF with splenomegaly and cystic masses of the spleen, nine were in the second and third decades of life. Five of the cystic masses were congenital or true cysts, two were tumors (1 cystic hemangioma and 1 cystic lymphangioma), one infectious (echinococcal), one a traumatic or false cyst, and one a cyst of unstated origin.[17] Four of the ten patients had left upper quadrant pain, two had left upper quadrant tenderness, and one had both left upper quadrant pain and tenderness; three were asymptomatic. Massive splenomegaly was present in eight (80%) of the ten patients. Two patients had progressive splenic enlargement: one had the traumatic cyst, and the other had the cystic hemangioma. One patient with an epithelial cyst had fever, massive splenomegaly, and a splenic friction rub. The echinococcal cyst was calcified. One cyst was aspirated percutaneously; the fluid was not diagnostic. The surgical indications for cystic disease included massive cysts, those with an infectious cause, involvement of the splenic hilum, and infected cysts.[18] Seven patients at UCSF with massive splenomegaly and the patient with the echinococcal cyst had a splenectomy. The cyst that was percutaneously aspirated was localized to one splenic pole, and the patient had a partial splenectomy. The one remaining patient had a small asymptomatic epithelial cyst and came to autopsy. The Armed Forces Institute of Pathology reviewed 52 patients with true and false splenic cysts and could not find reliable radiologic distinctions between the two.[19] Thus, etiologic uncertainty of cystic masses of the spleen may be another factor that dictates a diagnostic splenectomy for almost all these patients.

Splanchnic Vein Obstruction

Portal vein thrombosis occurred in 21 patients: 7 in this series and 14 during the second period of the study at UCSF (from 1937 to 1962). Splenic vein thrombosis occurred in 14 patients: 8 in the third period at UCSF

TABLE 6.—*Indications for Splenectomy in Patients With Splenomegaly**

		Indication for Splenectomy				
Disease	Patients, Total No.	Amelioration No. (%)	Hypersplenism No. (%)	Diagnostic No. (%)	Symptomatic No. (%)	% of Total
Hematologic	110	86	16	5	3	(65)
Hepatic	34	10	18	6	0	(20)
Infectious	10	3	2	5	0	(6)
Primary splenic	9	7	0	2	0	(5)
Other,† congestive, inflammatory	7	3	1	2	1	(4)
Total	170	109 (64)	37 (22)	20 (12)	4 (2)	(100)

*Data are for patients of all 3 series at UCSF plus those at SFGH. % of Total refers to percentage of total number of splenectomies for each disease group.
†Other refers to hepatic, infectious, and carcinomas.

(after 1962) and 6 in the second period. Portal vein thrombosis occurred in 11 children and 10 adults, whereas SVT occurred in 11 adults and only 3 children. Only 2 of the 21 patients with PVT showed an underlying cause (1 polycythemia vera and 1 alcoholic liver disease), and 3 had abnormal results on liver function tests. Recent imaging studies of PVT in children showed a characteristic shape of the portal vein and suggested a congenital basis for the disease,[20] but another recent study showed an ongoing prothrombotic state in the portal circulation and suggested an acquired basis for PVT.[21] Hypersplenism was found in 13 of 21 patients with PVT and in 8 of 14 patients with SVT, for a total of 21 (60%) of 35 patients. A review back to the turn of the century of patients with isolated SVT found 66% with splenomegaly but only 9% with hypersplenism.[22] Massive splenomegaly occurred in 5 patients with PVT and 2 with SVT at UCSF, for a total of 7 (20%) of 35 patients. Gastrointestinal bleeding occurred in only 4 patients with PVT and 2 patients with SVT at UCSF, for a total of 6 (17%) of 35 patients. Ascites occurred in 2 patients each with PVT and SVT at UCSF, for a total of 4 (11%) of 35 patients. Clearly, these patients at UCSF were relatively asymptomatic.[23]

Splenectomy was performed in 14 of 21 patients with PVT at UCSF; 6 did not have a splenectomy, and 1 died and was examined at autopsy. Splenectomy was performed in 9 of 14 patients with SVT; 4 did not have a splenectomy, and 1 died and was examined at autopsy. Thus, splenectomy was performed with almost the same frequency (67%) in PVT as in SVT (64%), even though the operation is contraindicated in patients with PVT.[23] The main procedure used in PVT to prevent recurrent variceal bleeding was a portal-systemic shunt operation.[23] It was used only once at UCSF, however, in a patient with many bleeding episodes from esophageal varices. Three of the four patients with SVT who did not have a splenectomy or who were examined at autopsy had apparent surgical contraindications: one patient had severe mental retardation, one was pregnant, and one had a history of multiple pulmonary emboli. The response to splenectomy in SVT was excellent: the surgical mortality was 0% and no postoperative complications or long-term gastrointestinal bleeding occurred. The overall mortality for all the patients with SVT was only 7%.[24]

Only 1 of the 14 patients with SVT at UCSF had pancreatitis, whereas in most reported series, the rate is more than 50%.[25] Splenic vein thrombosis with the classic triad of splenomegaly, gastrointestinal bleeding, and normal liver function test values occurred in only three patients (21%), all of whom had hypersplenism as well. One patient with SVT had an arteriovenous malformation of the splenic artery with an audible splenic bruit.[26] Another patient with SVT had an associated small aneurysm of the splenic artery, massive splenomegaly, and hypersplenism.[27] One patient with SVT had gastric varices without esophageal varices on endoscopy, the classic left-sided localized portal hypertension.[28] One patient at UCSF who bled after splenectomy had another classic finding of SVT, massive enlargement of the left gastroepiploic vein.[28] Thus, SVT has two different systems of collateral veins: the short gastric veins with gastric varices and the gastroepiploic veins with varices in the small or large bowel that can bleed. Most authors recommend splenectomy as the treatment of choice for SVT,[25] but others recommend a conservative approach in asymptomatic patients unless hemorrhage occurs.[29] If the SVT developed acutely—for example, after splenectomy or pancreatitis—anticoagulant drugs were recommended for the duration of obstruction.[29]

AIDS and Splenomegaly

Infections with HIV and splenomegaly at SFGH occurred in 44 (30%) of the total 148 patient, and in 30 (57%) of 53 patients with infectious disease. Of these 30 patients, 7 (23%) had massive splenomegaly, 5 of whom had infection with *M avium* complex. At UCSF, infections with HIV and splenomegaly occurred in only 8 (3%) of 301 patients. Three (38%) of these 8 patients had massive splenomegaly, two of whom had infection with *M avium* complex. The one patient at Santa Clara Valley Medical Center with HIV infection and massive splenomegaly also had infection with *M avium* complex.[4] Thus, 8 (73%) of the 11 patients with AIDS and massive splenomegaly had an associated infection with *M avium* complex. The greater incidence of infections with *M avium* complex at SFGH probably reflected a patient population with more advanced AIDS because infections with *M avium* complex occur only when the CD4 cell count is less than 0.10×10^9 per liter (<100 per µl).[30]

Human immunodeficiency virus infection resides in the lymphatic system and causes lymphadenopathy.[31] In the combined UCSF-SFGH series, lymphadenopathy occurred in 30 (79%) of the 38 patients with AIDS and splenomegaly. In addition, five of the eight patients with lymphoma at SFGH were infected with HIV.[32] Five of the AIDS patients at SFGH and Santa Clara Valley Medical Center[4] had diseases that occur particularly in immunocompromised hosts: disseminated histoplasmosis, cryptococcosis, cytomegalovirus disease, and disseminated *Pneumocystis carinii* disease.[33] One patient with AIDS at Santa Clara Valley Medical Center[4] had disseminated cat- scratch disease, and one patient with AIDS at SFGH had bacillary angiomatosis, diseases that have been redefined by the recent discovery of the protobacterium Rochalimaea.[34]

Hemoglobinopathy and Splenomegaly

Of the 13 patients with hemoglobinopathy and splenomegaly, 7 were adults. Five (38%) patients had massive splenomegaly, and nine patients (69%) had hypersplenism. Six patients (46%) had a splenectomy: two with thalassemia for hypersplenism and massive splenomegaly, two with hemoglobin SC disease for painful splenic infarctions, and two for splenic sequestration (1 with hemoglobin SS and 1 with hemoglobin SC disease).[35] Splenic sequestration has been reported in

adults with hemoglobin SC and sickle cell–thalassemia disease.[36] The two patients with splenic infarcts were both adults and had hemoglobin SC disease, which is being reported more frequently.[37] The patient with β^o-thalassemia–hemoglobin E had massive splenomegaly, a finding more frequent with β^o-thalassemia and absent production of hemoglobin A.[38]

Splenomegaly With Tumors Not Metastatic to the Spleen

Many of the patients with solid tumors and splenomegaly in this and all the series at UCSF (36 [92%] of 39 patients) did not have metastases to the spleen even on microscopic examination at autopsy or splenectomy. Yet, these tumors, mostly carcinomas of several different organs—kidney, pancreas, lung, breast, and hepatic metastases with unknown primary—seemed to be associated with splenomegaly as a component of the host response to cancer.[39] Clinical reports on this association were readily found in the literature,[40] particularly for patients with malignant melanoma.[41] With removal of the primary site of the malignant melanoma, the splenomegaly usually regressed.[42] In mice injected with tumor cells, colonies of cancer cells regularly developed, accompanied by expansion of their reticuloendothelial system and by splenomegaly.[43] Thus, the splenomegaly of tumors remote to the spleen could reflect an immunologic response of the host to the tumor.[44]

Splenectomy

The incidence of splenectomy in patients with splenomegaly at UCSF increased markedly over time: 4% from 1913 to 1936, 9% from 1937 to 1962, and 26% from 1963 to 1995. The low incidence of splenectomy in the earliest period at UCSF may reflect the initial development of the operation primarily for specific hematologic diseases.[45] The higher incidence of splenectomy in the later series may reflect the wider use and more liberal indications for the operation as its mortality rate dramatically declined. By 1910, Sutherland and Burghard successfully treated two patients with hereditary spherocytosis with splenectomy because "the spleen is actively engaged in the destruction of blood cells."[46 p1822] In 1916, Kaznelson, a precocious medical student in Prague, successfully applied this theory to the blood platelets by inducing his professor of surgery to perform a splenectomy in a patient with idiopathic thrombocytopenic purpura (ITP).[47] Before 1928, even the Mayo Clinic had a 10% mortality for 500 patients with splenectomy performed except in the "triumph of splenectomy" for ITP and hereditary spherocytosis (<5% mortality).[48] Now, the mortality for splenectomy, even for massive splenomegaly, is less than 1%.[49] Currently, ITP is the commonest hematologic indication for splenectomy.[45] The low incidence of splenectomy for ITP in all the series at UCSF (3 of 2,056 patients) partially reflects the low incidence of splenomegaly in ITP, about 2%.[50] The commonest disease for splenectomy at UCSF was hereditary spherocytosis: 16 (57%) of 28 patients from 1913 to 1936 and 59 (44%) of 133 patients from 1937 to 1962.

Previous reports cited lymphoma as the largest disease group for diagnostic splenectomy, usually about a third of these patients.[51] In the entire series at UCSF, only two patients had a diagnostic splenectomy for lymphoma. In the earliest series at UCSF in which lymphoma was the commonest hematologic disease associated with splenomegaly, none of those patients had a splenectomy. The current series had a 12% rate of diagnostic splenectomy (20 of 170 patients), similar to the 10% reported by others.[52] With detailed preoperative evaluation, the need for a diagnostic splenectomy could be reduced even further. Furthermore, the use of diagnostic splenectomy is tempered even more by the fear of overwhelming postsplenectomy infection and the frequent lack of a definitive diagnosis.[53] In this series at UCSF and SFGH of splenectomy for splenomegaly, 19% of the patients had massive splenomegaly. In a recent study from the National Institutes of Health of splenectomy for massive splenomegaly, the commonest disease group for which a splenectomy was done was overwhelmingly hematologic disease (96%),[54] compared with 61% at UCSF.

Hospital-based Patients and the Incidence of Splenomegaly: Why So Low?

The incidence of splenomegaly in the four series at UCSF was about 1% before 1963 and about 0.3% after 1963. In contrast, the incidence of splenomegaly in healthy first-year college students was found to be 3%.[55] Even in office-based prospective series on splenomegaly,[2,3] the incidence of splenomegaly was 2% and 5%, respectively. One explanation for this discrepancy is the nature of the study in the healthy college students: two expert hematologists were prospectively and specifically determining the incidence of splenomegaly. Similarly, Lipp and colleagues in their study[2] were prospectively "looking for" splenomegaly. At UCSF, the studies were retrospective tabulations of splenomegaly detected by physicians with no direct interest in the spleen or its enlargement. This underreporting of splenomegaly (the denominator) may explain the "high" incidence of massive splenomegaly (the numerator) in the studies at UCSF, particularly the average of 22% found for chronic liver disease in the four studies at UCSF and the 50% found for CML in the present series.

Diagnostic Evaluation of Unexplained Splenomegaly

Any patient who presents with unexplained splenomegaly should have an evaluation with respect to its cause, particularly if cancer is in the differential diagnosis. A complete history and thorough physical examination may establish the diagnosis.[56] The physician should review the laboratory test results, the imaging studies, and particularly the peripheral blood smear.[57] If benign disease is suggested by the evaluation, patients with splenomegaly can simply be observed periodically.[55] A lymph node biopsy should be done, particularly if lymphadenopathy is present and a malignant lesion is suspected.[58] For patients with hematologic associations, bone marrow

aspiration and biopsy may be the invasive procedure of choice; for hepatic associations, a percutaneous liver biopsy; and for infectious disease, a lymph node biopsy, before any consideration of a diagnostic splenectomy.[59] Percutaneous splenic procedures had been limited by the mortality associated with splenic biopsy and the lack of tissue architecture associated with fine-needle aspiration.[60] Paradoxically, percutaneous liver biopsy for splenomegaly was reported to be more valuable in the tropics than percutaneous splenic procedures.[61] If these invasive procedures fail to establish a cause for the splenomegaly, the ultimate diagnostic test of laparotomy and splenectomy may be required.[59] Splenic structure is virtually unchanged in its evolution from primitive fish, however.[62] So the spleen may be important for our survival and not be readily disposable, as evidenced by overwhelming postsplenectomy infections.[53]

Acknowledgment

I am grateful to Lloyd H. Smith Jr, MD, formerly associate editor for THE WESTERN JOURNAL OF MEDICINE, for his critical review of the manuscript and for his many helpful suggestions.

REFERENCES

1. Osler W. Discussion on splenic enlargements other than leukaemic. BMJ 1908; 2:1151–1158

2. Lipp WF, Eckstein EH, Aaron AH. Clinical significance of the palpable spleen. Gastroenterology 1944; 3:287–291

3. Schloesser LL. Diagnostic significance of splenomegaly. Am J Med Sci 1963; 245:84–90

4. O'Reilly RA. Splenomegaly at a United States county hospital: diagnostic evaluation of 170 patients. Am J Med Sci 1996; 312:160–165

5. O'Reilly RA. Splenomegaly in 2,505 patients at a large university medical center from 1913 to 1995. Part 1—1913-1962: 2,056 patients. West J Med 1998; 169:78–87

6. Press OW, Press NO, Kaufman SD. Clinical review: evaluation and management of chylous ascites. Ann Intern Med 1982; 96:358–364

7. Jandl JH. Blood: textbook of hematology. 2nd ed. Boston (Mass): Little, Brown; 1985, pp 407–432

8. Weintraub LR. Splenectomy: who, when, and why? Hosp Pract 1994 Jun 15; pp 27–34

9. Jacobs P, Wood L, Dent DM. Splenectomy in the chronic myeloproliferative syndromes—A retrospective risk-versus-benefit analysis. South Afr J Med 1992; 81:499–503

10. Anger BR, Seifried E, Scheppach J, Heimpel H. Budd-Chiari syndrome and thrombosis of other abdominal vessels in the chronic myeloproliferative diseases. Klin Wochenschr 1989; 67:818–825

11. Singh AK. A prospective study of the evolution of chronic lymphocytic leukaemia. Leuk Lymphoma 1992; 7:87–97

12. Levin M. Acute hypersplenism and thrombocytopenia: a new presentation of disseminated mycobacterial infection in patients with acquired immunodeficiency syndrome. Acta Haematol 1994; 91:28–31

13. Johnson PC, Khardori N, Najjar AF, Butt F, Mansell PWA, Sarosi GA. Progressive disseminated histoplasmosis in patients with acquired immunodeficiency syndrome. Am J Med 1988; 85:152–158

14. Sato T, Ozawa T, Kikuchi M, et al. A case of progressive systemic sclerosis associated with mutilans-type arthropathy and suspected Felty's syndrome [Japanese]. Ryumachi 1990; 30:53–59

15. Arellano L, Segovia M, Otaiza E, Velasco A. Complicated primary splenic cyst: a clinical case [Spanish]. Rev Med Chil 1990; 118:675–678

16. Kyllerman M, Conradi N, Månsson JE, Percy AK, Svennerholm L. Rapidly progressive type III Gaucher disease: deterioration following partial splenectomy. Acta Paediatr Scand 1990; 79:448–453

17. Urrutia M, Mergo PJ, Ros LH, Torres GM, Ros PR. Cystic masses of the spleen: radiologic-pathologic correlation. Radiographics 1996; 16:107–129

18. Dawes LG, Malangoni MA. Cystic masses of the spleen. Am Surg 1986; 52:333–336

19. Dachman AH, Ros PR, Murari PJ, Olmsted WW, Lichtenstein JE. Nonparasitic splenic cysts: a report of 52 cases with radiologic-pathologic correlation. AJR Am J Roentgenol 1986; 147:537–542

20. Ando H, Kaneko K, Ito F, Seo T, Watanabe Y, Ito T. Anatomy and etiology of extrahepatic portal vein obstruction in children leading to bleeding esophageal varices. J Am Coll Surg 1996; 183:543–547

21. Violi F, Ferro D, Basili S, et al. Ongoing prothrombotic state in the portal circulation of cirrhotic patients. Thromb Haemost 1997; 77:44–47

22. Sutton JP, Yarborough DY, Richards JT. Isolated splenic vein occlusion: review of literature and report of an additional case. Arch Surg 1970; 100:623–626

23. Cohen J, Edelman RR, Chopra S. Portal vein thrombosis: a review. Am J Med 1992; 92:173–182

24. Simpson WG, Schwartz RW, Strodel WE. Splenic vein thrombosis. South Med J 1990; 83:417–421

25. Glynn MJ. Isolated splenic vein thrombosis. Arch Surg 1986; 121:723–725

26. Björkman SE. On the occurrence of a vascular murmur over greatly enlarged spleens. J Intern Med 1953; 145:79–83

27. Mattar SG, Lumsden AB. The management of splenic artery aneurysms: experience with 23 cases. Am J Surg 1995; 169:580–584

28. Bunt TJ, Hackler MT, Greene FL. Isolated splenic vein thrombosis: the curable variceal hemorrhage. South Med J 1983; 76:936–938

29. Rahmouni A, Mathieu D, Golli M, et al. Value of CT and sonography in the conservative management of acute splenoportal and superior mesenteric venous thrombosis. Gastrointest Radiol 1992; 17:135–140

30. Horsburgh CR Jr. *Mycobacterium avium* complex infection in the acquired immunodeficiency syndrome. N Engl J Med 1991; 324:1332–1338

31. Pantaleo G, Graziosi C, Demarest JF, et al. HIV infection is active and progressive in lymphoid tissue during the clinically latent stage of disease. Nature 1993; 362:355–358

32. Guidano G, Carbone A. AIDS-related lymphomas: from pathogenesis to pathology. Br J Haematol 1995; 90:235–243

33. Rockley PF, Wilcox CM, Moynihan M, Hewan-Lowe K, Schwartz DA. Splenic infection simulating lymphoma: an unusual presentation of disseminated *Pneumocystis carinii* infection. South Med J 1994; 87:530–536

34. Adal KA, Cockerell CJ, Petri WA Jr. Cat scratch disease, bacillary angiomatosis, and other infections due to rochalimaea. N Engl J Med 1994; 330:1509–1515

35. Sears DA, Udden MM. Splenic infarction, splenic sequestration, and functional hyposplenism in hemoglobin SC disease. Am J Hematol 1985; 18:261–268

36. Solanski DL, Kletter GG, Castro O. Acute splenic sequestration crises in adults with sickle cell disease. Am J Med 1986; 80:985–990

37. Aquino VM, Norvell JM, Buchanan GR. Acute splenic complications in children with sickle cell-hemoglobin C disease. J Pediatr 1997; 130:961–965

38. Nguyen CK, Le TT, Duong BT, Dinh PH, Ta TH, Tran HH. Beta-thalassemia-haemoglobin E disease in Vietnam. J Trop Pediatr 1990; 36:43–45

39. Roberts JG, Wisbey M, Leach KG, Baum M. Spleen size in patients with breast cancer [Abstract]. Br J Cancer 1975; 31:262

40. DeLand FH. The value of determining splenic weight in radionuclide imaging [Abstract]. J Nucl Med 1973; 14:390

41. Ikonopisov RL, Oreshkov VI. Possible immunological significance of hepatomegaly and splenomegaly as recorded by hepatic gamma scanning in patients with malignant melanoma. Tumori 1974; 60:99–104

42. Klingensmith WC III. Resolution of increased splenic size and uptake of ^{99m}Tc-sulfur colloid following removal of a malignant melanoma. J Nucl Med 1974; 15:1203–1204

43. Old LJ, Benacerraf B, Clarke DA, Carswell EA, Stockert E. The role of the reticuloendothelial system in the host reaction to neoplasia. Cancer Res 1961; 21:1281–1300

44. Berjian RA, Parthasarathy KL, Didolkar MS, Bakshi SP, Moore RH. Significance of ^{99m}Tc- sulfur colloid splenic image in malignant melanoma. J Surg Oncol 1980; 13:53–60

45. Schwartz SI. Role of splenectomy in hematologic disorders. World J Surg 1996; 20:1156–1159

46. Sutherland GA, Burghard FF. The treatment of splenic anaemia by splenectomy. Lancet 1910; 2:1819–1823

47. Kaznelson P. Verschwinden der hämorrhagischen Diathese bei einem Falle von 'essentieller Thrombopenie' (Frank) nach Milzexstirpation—Splenogene thrombolytische Purpura. Wien Klin Wochenschr 1916; 29:1451–1454

48. Mayo WJ. A review of 500 splenectomies with special reference to mortality and end results. Ann Surg 1928; 88:409–415

49. Farid H, O'Connell TX. Surgical management of massive splenomegaly. Am Surg 1996; 62:803–805

50. Doan CA, Bouroncle BA, Weisman BK. Idiopathic and secondary thrombocytopenic purpura: clinical study and evaluation of 381 cases over a period of 28 years. Ann Intern Med 1960; 53:861–876

51. Hermann RE, DeHaven KE, Hawk WA. Splenectomy for the diagnosis of splenomegaly. Ann Surg 1968; 168:896–900

52. Cronin CC, Brady MP, Murphy C, Kenny E, Whelton MJ, Hardiman C.

Splenectomy in patients with undiagnosed splenomegaly. Postgrad Med J 1994; 70:288–291

53. Spelman DW. Postsplenectomy overwhelming sepsis: reducing the risks [Editorial]. Med J Aust 1996; 164:648

54. Danforth DN Jr, Fraker DL. Splenectomy for the massively enlarged spleen. Am Surg 1991; 57:108–113

55. McIntyre OR, Ebaugh FG Jr. Palpable spleens in college freshmen. Ann Intern Med 1967; 66:301–306

56. Eichner ER, Whitfield CL. Splenomegaly: an algorithmic approach to diagnosis. JAMA 1981; 246:2858–2861

57. Rosenthal DS. Case records of the Massachusetts General Hospital (Case 48-1985). N Engl J Med 1985; 313:1405–1412

58. Faller DV. Diseases of the lymph nodes and spleen. In: Wyngaarden JB, Smith LH Jr, Bennett JC, editors. Cecil: textbook of medicine, 19th ed. Philadelphia (Pa): WB Saunders; 1992, pp 978–985

59. Videbaek A, Christensen BE, Jønsson V. The spleen in health and disease. Chicago (Ill): Year Book Medical Publishers; 1982, p 182

60. Cavanna L, Civardi G, Fornari F, et al. Ultrasonically guided percutaneous splenic tissue core biopsy in patients with malignant lymphomas. Cancer 1992; 69:2932–2936

61. Hutt MSR, Lowenthal MN. Chronic splenomegaly in the tropics. Trop Doctor 1974; (4):51–55

62. Coetzee T. Review article: clinical anatomy and physiology of the spleen. South Afr Med J 1982; 61:737–746

Articles

Insulinoma—Experience from 1950 to 1995

MILANA P. BOUKHMAN, JOHN H. KARAM, MD, JOHN SHAVER, MD, ALLAN E. SIPERSTEIN, MD, QUAN-YANG DUH, MD, *and* ORLO H. CLARK, MD

Insulinomas are rare tumors that originate from the islet cells of the pancreas. The purpose of this study was to analyze our experience in patients with insulinoma and present our approach to these patients. Medical records of 67 patients treated at the University of California, San Francisco (UCSF) Medical Center, 56 surgically and 11 medically, from 1954 to 1995 were retrospectively reviewed. Presenting symptoms, physical findings, laboratory data, pre and intraoperative localization studies, operative management , operative success, and post-operative complications were analyzed. Among the entire cohort, there were 11 patients with Multiple Endocrine Neoplasia type I (MEN 1) and 7 patients with multiple tumors. 46 out of 48 patients (96%) having first operations for benign tumors and 5 out of 8 patients (63%) having reoperations for benign tumors were successful, as were 6 out of 12 patients (50%) having operations for islet cell carcinoma. Overall, preoperative localization studies were positive in only 46% of patients and therefore failed to improve our surgical outcome. Careful palpation with intraoperative ultrasonography gave the best localization results. Enucleation of solitary tumors is curative in sporadic cases and gives the lowest complication rate. In patients with MEN1, subtotal pancreatectomy with enucleation of tumors from the pancreatic head and uncinate process is recommended over simple enucleation because of frequent multiple tumors.

(Boukhman MP, Karam JH, Shaver J, Siperstein AE, Duh Q-Y, Clark OH. Insulinoma—Experience from 1950 to 1995. West J Med 1998; 169:98–104)

Although rare, insulinoma is the most common tumor of the endocrine pancreas, occurring in about one person per million population per year. Langerhans, while a medical student, described pancreatic islets and their possible function 70 years before the first patient with an insulinoma was reported.[1,2] The association between hyperinsulinism and a functional islet cell tumor was established by Wilder et al[3] in 1927; he performed an operation on a patient with hypoglycemia and found an islet cell carcinoma with hepatic metastases. Whipple thought that symptoms of hypoglycemia provoked by fasting, a circulating glucose level below 50 mg/100 cc at the time symptoms presented, and relief of symptoms with glucose administration were the basis for making the diagnosis of insulinoma, thus establishing "Whipple's Triad."[4] The first surgical cure of an islet cell adenoma was achieved by Graham in 1929.[5]

Islet cell tumors occur predominantly in the pancreas but also in the duodenum and peripancreatic nodes. 99% of insulinomas are found within the pancreas. The incidence of islet cell tumors is estimated to be less than 1-1.5 cases per 100,000 of the general population. Approximately 50% of islet cell tumors are insulinomas, 30% gastrinomas, 10%-15% vasoactive intestinal peptide secreting tumors (VIPomas), and 5-10% other tumor types, including glucagonomas, somatostatinomas, and pancreatic polypeptide-secreting tumors (PPomas).[6,7]

Our report retrospectively analyzes the clinical and diagnostic features, surgical course, pathologic findings, and long-term outcome of 67 patients with insulinoma.

Patients and methods

During a 41 year period between 1954 and 1995, 67 patients were referred to UCSF Medical Centers with a biochemical diagnosis of organic hyperinsulinism. There were 22 male and 45 female patients. Their ages ranged from two weeks to 85 years, with a mean age of 46 years and a peak incidence from 40 to 50. (Figure 1). Fifty-one of these patients were treated since 1975, a time when ultrasound and CT scanning became available.[8] Sixteen patients were treated between 1954 and 1975. Such disparity in the numbers of patients seen in these two 20-year periods could be due to the increased

From the Department of Surgery, University of California, San Francisco/Mt. Zion Medical Center, California.

Address reprint requests to: Orlo H. Clark, MD, Chief of Surgery, University of California, San Francisco/Mt. Zion Medical Center, 1600 Divisadero St., San Francisco, Ca. 94115

Supported in part by the Edwin Zeller Fund and Friends of UCSF/Mt. Zion Endocrine Surgical Oncology Research.

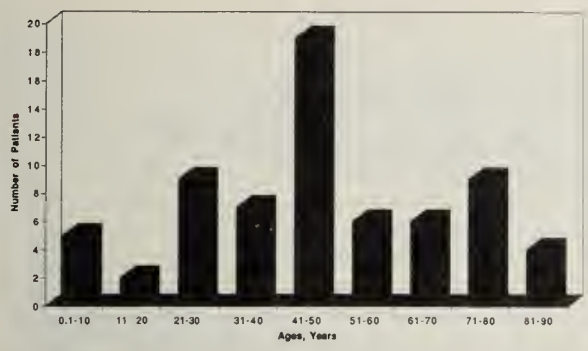


Figure 1.—Age distribution in patients.

awareness of this condition, more accurate diagnosis and more patient referral.

A total of 68 operations were performed in the 56 patients treated operatively. Out of those, 54 were primary and 14 were reoperations (nine first and five second reoperations). Seven of these patients had their initial pancreatic explorations elsewhere and were referred for persistent or recurrent insulinoma. Eleven patients (16%) had MEN 1, and seven of these MEN 1 patients or 63% had multiple insulinomas. Ten patients (15%) had malignant insulinomas, including one-third of patients with MEN 1. Among the 16 patients in the 1954–1975 group, four patients had MEN 1 and three patients had cancer. Among the 51 patients in the 1975–1995 group, seven patients had MEN 1 and seven patients had cancer. Five patients had hyperplasia, three being children aged two weeks, one month and three months, and two being adults aged 36 years and 70 years. Eleven patients were treated with medicine only.

Results

Symptoms

Symptoms of hypoglycemia including hunger, headache, palpitations, and confusion occurred at various times, but in 39 of the 67 patients occurred before meals or during fasting. In nine patients, symptoms were precipitated by exercise. Six patients experienced symptoms post prandially and five patients had continuous symptoms unrelated to eating. To avoid falling into comas, four patients set alarms in order to awaken and eat during the night. Six patients had histories of being unable to awaken in the morning due to severe hypoglycemia. Many patients exhibited hysterical and bizarre behavior with weakness and tremors, and nine had been treated for seizures before a proper diagnosis was made. Similar symptoms have been reported by others. [9–11] The incidences of the various symptoms are listed in Figure 2.

Overall, 75% of patients presented with altered mental states and/or confusion. The duration of symptoms ranged from five minutes to several hours. A few patients, including three infants, had clinical manifestations such as lethargy and irritability, and two infants had convulsions. Six of the patients with insulinoma were being treated by a psychiatrist.

Since many patients frequently eat to avoid symptoms, it is surprising that only 14% of the patients in our study gained weight. For 45 patients, the clinical manifestations of hypoglycemia became more severe and increased in frequency the longer the tumors were present, whereas in 14 patients symptoms were not progressive.

Among the 60 patients, where the information was available, the duration of symptoms prior to diagnosis

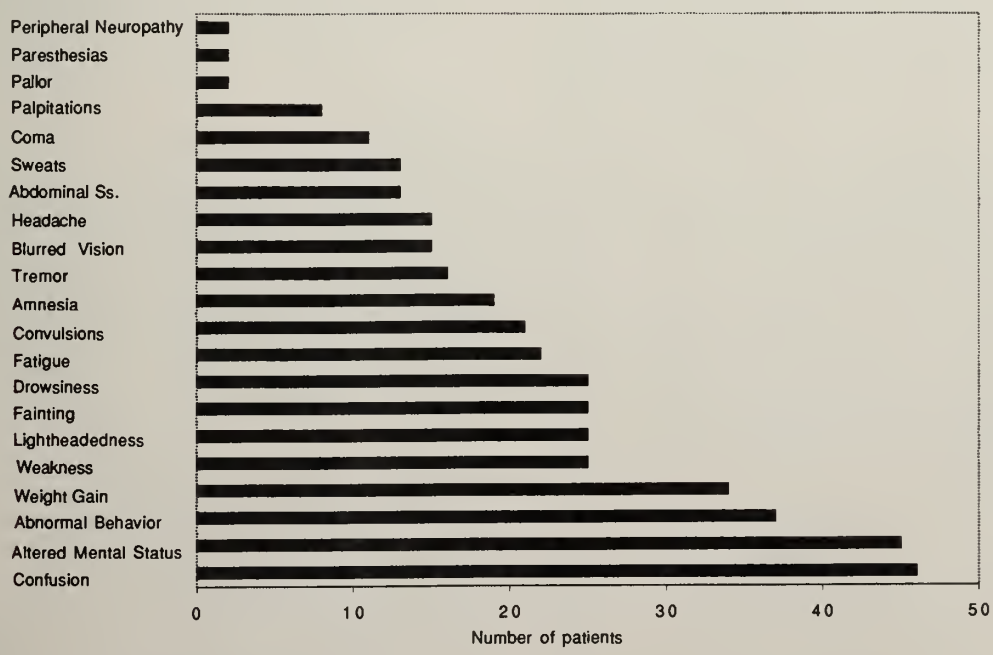


Figure 2.—Symptoms during hypoglycemic spells.

TABLE 1.—*Test Results of the Various Localization Techniques for Insulinoma.*

Technique	*Test Results*			
	TP	*TN*	*FP*	*FN*
CT	13	1	1	20
Arteriography	14		1	15
MRI	3		1	4
MRI w/Gadolinium	3		1	2
Pre-operative Ultrasound	4			2
Intra-operative Ultrasound	9	1		1
THPVS	7			3
Palpation	42	1		14

THPVS=Transhepatic Portal Venous Sampling; TP=True Positive; TN=True Negative; FP=False Positive; FN=False Negative

ranged from one hour in a newborn to 34 years, with a mean duration of 3.8 years. The diagnosis of insulinoma was delayed for various reasons, including the infrequency of attacks, and the fact that the symptoms could be aborted by eating. Two of our patients were retarded, possibly due to delay in diagnosis or treatment of hypoglycemia.[4,12]

Diagnosis

The knowledge that the fasting insulin-to-glucose ratio was higher than 0.3 was helpful in making the diagnosis in 48 of our patients. The C-peptide levels in all of our patients ranged from 0.9 to 8.1 (normal fasting is 0.8 to 4.0 ugs/L). Fasting with determination of insulin-to-glucose ratios was used in 37 patients and various provocative tests were used infrequently. Glucagon and tolbutamide tests were both used in 23% of the patients, mostly in the early years of the study. The tolbutamide test is no longer done. In most patients the fasting glucose-to-insulin ratio with an elevated C-peptide and a negative urinary sulfonylurea level were sufficient for making the diagnosis.

The blood sugar levels recorded in our patients were under 10 mg/100 ml in four patients, between 10 and 20 mg/100ml in 17 patients, between 21 and 30 in 25 patients, between 31 and 40 in 12 patients, between 41 and 50 in six patients, and above 50 in two patients.

Among our patients with MEN 1, other endocrine syndromes or pathology included: hyperparathyroidism(10), pituitary adenomas (6), two of which were prolactinomas, gastrinomas (5), thyromegaly (2), papillary carcinoma of thyroid (1), hyperaldosteronism (1), and hypotestosteronism (1).

Localizing studies

Preoperative localization studies were done in 56 patients. The results of the preoperative localization studies including arteriography, transhepatic portal venous sampling (THPVS), computed tomography (CT), Magnetic Resonance Imaging (MRI) with gadolinium are shown in Table 1. Intraoperative ultrasonography was positive in 90% of the cases, and intraoperative palpation was positive in 75%. Among 10 tumors identified by intraoperative ultrasonography, there were no false-positive studies. Four insulinomas that were non-palpable or non-visible were identified by intraoperative ultrasonography. These adenomas were all soft in consistency and were not palpable even after being identified by ultrasound. CT scanning was primarily used in our patients to identify large tumors with possible liver or nodal metastases. Our data document that intraoperative techniques including palpation and ultrasound are considerably more reliable for identifying insulinoma than any preoperative study.

In patients from whom this information was available, the median diameter of the 52 solitary tumors was 1.6 cm. Twelve patients had tumors less than 1 cm in maximum diameter. Two patients had tumors larger than 6 cm. The size distribution of the insulinomas is shown in Figure 3.

Seven of the 67 patients, all with MEN 1, had multiple tumors (mean number 7) ranging from microscopic to 3 cm in diameter (mean size 2.1 cm). Three of these patients had more than 10 tumors , one patient had nine and one patient had two. Among our entire group of patients, the insulinomas were evenly distributed throughout the pancreas (38% head, 37% body, and 25% tail). None of the insulinomas identified in our patients was located outside the pancreas, although one patient remained hypoglycemic after a Whipple operation for islet cell cancer. Among our 67 patients, 10 (15%) had malignant insulinoma, which is comparable to a 10% malignancy rate reported in other literature. [8,10,11] Four of the 10 patients with islet cell carcinomas had MEN 1 and two of these patients also had gastrinomas. Eight patients had metastases, four in the lymph nodes, two in the lower abdomen, one in the brain and one in the lung. Nesidioblastosis was identified in three children and two adults.

Treatment

Preoperative treatment

After the diagnosis was established, patients were maintained on frequent feedings to reduce the risk of hypoglycemic episodes. Diazoxide was used in 41 patients. In 34 patients, there was a favorable response; however, 14 patients had complications [palpitations (13), hirsutism (5), edema (5), nausea (2), gastrointestinal discomfort (2), elevated uric acid (2)], and seven patients failed to respond. Five patients had complications so severe that they needed to discontinue diazoxide. Thus, diazoxide was successful in only 29 patients out of 41. Other pre-operative medical treatment included somatostatin in five patients, dilantin in four patients and chemotherapy in one patient.

Surgical treatment and outcome

Sixty-eight surgical procedures were performed in 54 patients, including enucleation of the insulinoma in 40 patients, distal pancreatectomy in 11, subtotal pancreatectomy in 12, Whipple procedure in four and one nega-

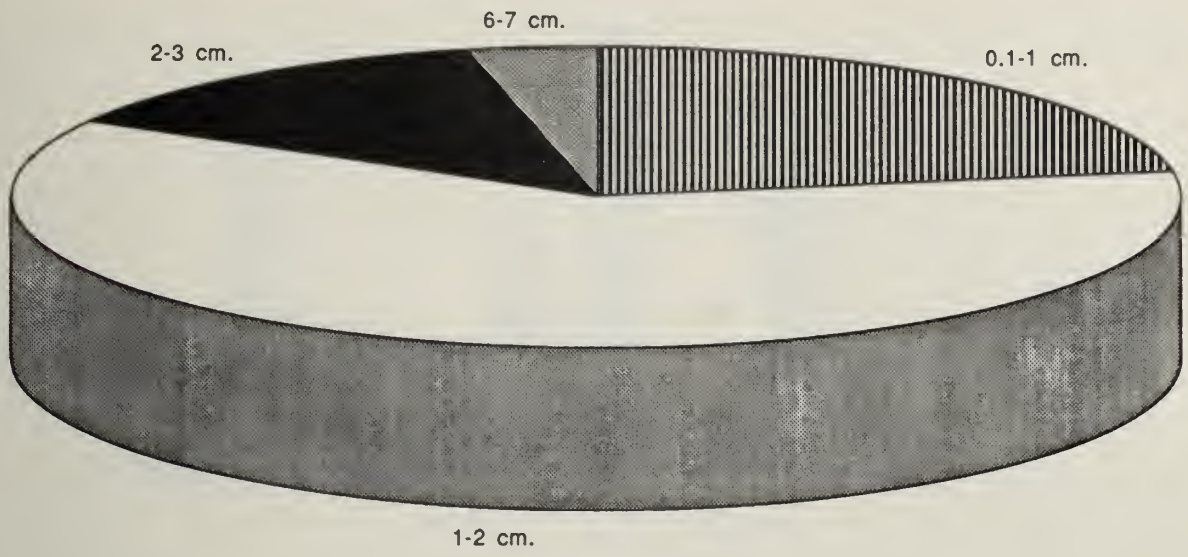


Figure 3.—Size distribution of insulinomas.

tive exploration with biopsy only. In four patients (two initial and two reoperations), no insulinoma or abnormal pancreatic tissue was identified or removed. Splenectomy was performed in 24% of all these patients and in 55% having distal pancreatectomy.

Eleven of our 68 operations (16%) were unsuccessful, six in patients who had reoperations. (Table 2). Six of these patients had MEN 1, three of whom had malignant tumors, five of whom had sporadic disease, and one of whom had a malignant tumor. Multiple tumors or nesidioblastosis accounted for four failures (two with MEN 1 and two with sporadic disease). Successful operations ensued in 89% of our patients having an initial pancreatic exploration at our medical centers, including patients with cancer, and in 96% of patients having initial operations and benign solitary tumors. Two patients died 17 days and 25 days after operation due to complications. One patient, 47 years old, had MEN 1 and a malignant insulinoma as well as hyperplasia/nesidioblastosis, and the other, 85 years old, had nesidioblastosis. Nine patients underwent reoperation for persistent (8) or recurrent (1) disease. In the patient with recurrence, symptoms appeared 18 years following her initial procedures. This fascinating yet unfortunate patient was originally thought to have a "benign" insulinoma, but hypoglycemia recurred after 18 years. At reoperation a Whipple procedure was unsuccessful, and she subsequently died of brain and lung metastases. Eight other patients underwent a first reoperation because of the persistent hyperinsulinism or recurrence within eight months. Unfortunately, three were not cured.

TABLE 2.—*Patients Who Underwent a Failed Surgical Exploration for Insulinoma.*

Patients	*MEN*	*Reason for Status*	*Pathology Exploration*	*Age*	*Sex*	*Operation*	*# tumors**	*Reasons for Failure*	*Histology*
#1	MEN 1	Persistent	Malignant	28	F	Subtotal Pancreatectomy	>10	2 Missed tumors	Multiple Adenomas
#2	MEN 1	Persistent	Benign	36	M	Subtotal Pancreatectomy	N/A	2 Hyperplasia	Hyperplasia
#3	MEN 1	Persistent	Malignant	43	M	Exploration only	N/A	2 No tumor found	Insulinoma
#4	MEN 1	Primary	Benign	36	M	Distal Pancreatectomy	N/A	1 Hyperplasia	Hyperplasia
#5	MEN 1	Primary	Benign	31	F	Subtotal Pancreatectomy	>10	1 Missed tumors	Insulinoma
#6	MEN 1	Primary	Malignant	28	F	Enucleation	>10	1 Missed tumors	Multiple Adenomas
#7	MEN 0	Persistent	Benign	0.8	F	Subtotal Pancreatectomy	N/A	1 Nesidioblastosis	Nesidioblastosis
#8	MEN 0	Persistent	Benign	41	F	Distal Pancreatectomy	N/A	2 No tumor found	Insulinoma
#9	MEN 0	Recurrent	Malignant	49	F	Whipple	N/A	3 Ectopic tumor	N/A
#10	MEN 0	Primary	Benign	4	F	Subtotal Pancreatectomy	N/A	1 No tumor found	Negative
#11	MEN 0	Primary	Benign	0.8	F	Subtotal Pancreatectomy	N/A	1 Nesidioblastosis	Nesidioblastosis

1=Initial Operation; 2=First Reoperation; 3=Second Reoperation

*Number of the exploration for insulinoma.

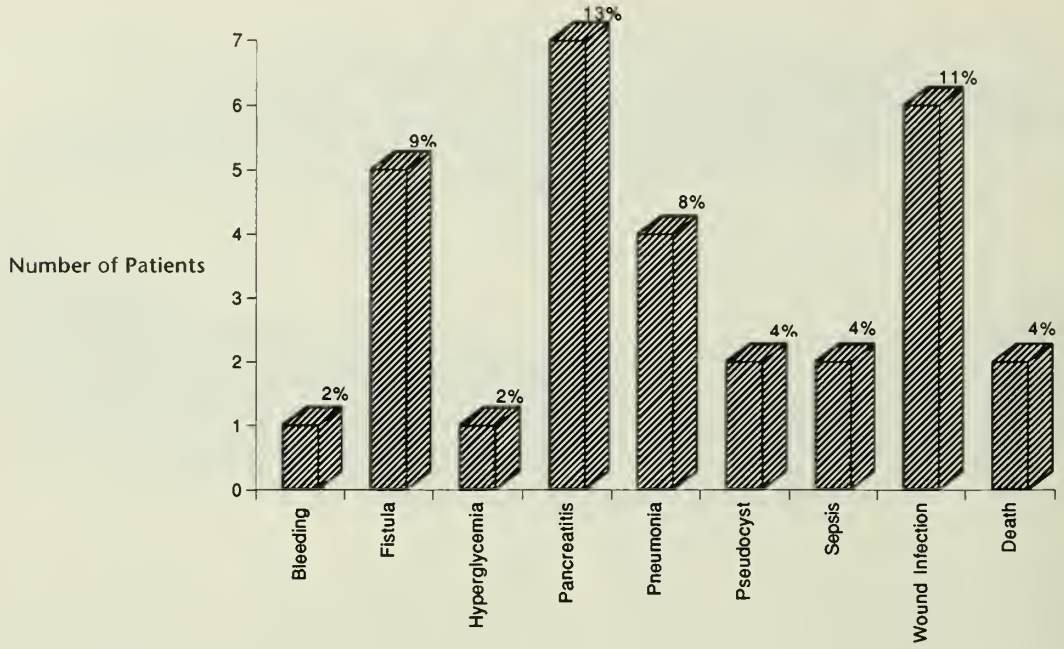


Figure 4.—Postoperative complications after 23 (43%) of 54 operations.

One infant with nesidioblastosis and hyperinsulinism had persistent hypoglycemia, even after a subtotal pancreatectomy. During the second operation, half of the 5% of the pancreas that remained was resected. After a Whipple procedure his hyperinsulinism and hypoglycemia resolved, but he requires insulin.

One patient with MEN 1 and insulinoma and gastrinoma had persistent disease after one malignant insulinoma was enucleated. Unfortunately, even though additional metastases were found and removed during a second operation and distal pancreatectomy, her hyperinsulinism persisted. She subsequently was cured after a Whipple procedure and liver resection when additional tumors were found in the head of her pancreas and liver. This patient also requires insulin.

A third patient underwent a second pancreatic operation after a distal pancreatectomy with negative histology. The patient remained hypoglycemic after a near total pancreatectomy, as no tumor was found. She subsequently had a Whipple procedure and a 1.3 cm tumor was removed. She is diabetic and requires insulin.

Five other patients underwent reoperation for persistent hyperinsulinism. Four were successfully treated and are euglycemic: Two had distal pancreatectomy and two had tumors enucleated from the uncinate process. One of these five patients required a second reoperation and had a malignant islet cell tumor removed.

Among 14 patients who required reoperations at UCSF (nine after an initial reoperation and five after two reoperations), only nine patients were successfully treated. The reason for the eleven unsuccessful operations in patients having primary (2) or reoperations (9) include: missed tumors (seven patients) and hyperplasia/nesidioblastosis (four patients). Four of these patients had malignant tumors. Among the seven failed operations due to missed tumors, two were performed on a patient with both malignancy and multiple tumors, and one was performed on a patient with metastatic islet cell tumor with no primary pancreatic islet cell tumor identified. (Table 2)

Sixty-five of 67 patients survived one or more operations. Of these 65 patients, 62 are no longer hyperinsulinemic but four patients are diabetic after subtotal or total pancreatectomy. Among the three surviving patients who remain hypoglycemic, one had extensive metastases and two elected not to undergo a reoperation.

The overall outcomes in terms of the operative success were similar between the 1954–1975 and the 1975–1995 treatment groups. For the 1954–1975 group, 14 out of the 18 operations (78%) performed were successful, as compared to 43 out of the 50 operations (86%) for the 1975–1995 group. Out of the four failed operations for the 1954–1975 treatment group, two were initial and two were second operations. The range of the procedures performed was also similar between the two groups. In the 1954–1975 group, enucleation was performed in eight (44%) patients, distal pancreatectomy in four (22%) patients, subtotal in three (17%) patients, total in one (6%) patient, and Whipple procedure in two (11%) patients. In the 1975–1995 group, enucleation was performed in 32 (64%) patients, distal pancreatectomy in seven (14%) patients, subtotal pancreatectomy in nine (18%) patients, and Whipple procedure in two (4%) patients.

Medical treatment and outcome

Eleven of the 67 patients with insulinoma were treated with medicine only. Nine of these patients chose not to undergo operation due to their satisfactory maintenance

with diazoxide therapy; only two (12 and 22 years old) of the 11 experienced significant complications of the diazoxide therapy; two other patients did not undergo an operation due to serious pre-existing medical conditions. One of these two patients had liver cancer with metastases and died three weeks after the diagnosis of his insulinoma. The other patient had metastases to lung and brain and chose not to undergo an operation.

Complications

Among the 54 patients having initial operations, complications (fistula, hemorrhage, sepsis, pleural effusion, etc., excluding diabetes) occurred in 43%, as illustrated in Figure 4. The post operative complication rate rose to 55% (five out of nine patients) in patients after a first reoperation and to 60% in those requiring second reoperations (three out of five patients). Diabetes mellitus developed as a result of near or total pancreatectomy in one patient who underwent one reoperation and in three out of the four patients (75%) who underwent second reoperations.

Complications differed depending upon the surgical procedure employed and were more common during the initial period of this study. As expected, more extensive pancreatic resection was associated with more complications. Thirty-five percent who were treated with enucleation had complications versus 69% and 75% with complications after subtotal and distal pancreatectomies, respectively. Enucleation of tumors from the head and uncinate process were associated with more complications. The higher incidence of complications such as wound infection, pneumonia and fistula that developed after subtotal or distal pancreatectomy than after enucleation documents that enucleation is a safer procedure.

The four patients who required reoperation for complications were all treated after 1975. In three of them, those complications had arisen after the first reoperation: two of these three were enucleations from the uncinate process, and one was subtotal pancreatectomy with enucleation from the head. Although the numbers are small, this data suggests that enucleations from the uncinate process and the pancreatic head region seem to pose particular dangers in terms of complications. Out of the whole patient cohort, only four patients underwent enucleations from the uncinate process, and two of them had to undergo additional operations because of complications: one patient had small bowel obstruction with abdominal adhesions and another one had thrombus formation, infection and pseudocyst. In one of those four patients, there was a complication of five pseudocysts into the stomach as a result of the primary enucleation from the tail. These were successfully treated at a subsequent operation.

In the 1954–1975 treatment group only three patients (19%) had complications due to surgery, compared to 27 patients (54%) in the 1974–1995 group.

There were two deaths (one operative). Both occurred after 1975. One, an 85-year-old woman, died 25 days after her initial subtotal pancreatectomy for nesidioblastosis after being transferred to a chronic care facility. At autopsy she was found to have a pancreatic abscess. A 47-year-old woman expired 17 days after her initial exploration and gastro-jejunostomy due to metastatic insulinoma.

Discussion

Our experience at UCSF medical centers documents that 89% of patients having initial pancreatic exploration for insulinomas are successfully treated, including 96% (46 out of the 48) with benign solitary tumors. Similar results have been reported by others.[13,14] Among the patients having initial pancreatic exploration for insulinoma, 60% (three out of five) with multiple tumors and 86% (six out of seven) with malignant tumors are successfully treated. In patients who had positive localization procedures, the success rate was 85% (18 patients) versus a success rate of 90% when tests were negative (18 patients) or not done (11 patients). Preoperative localization studies such as CT scans do provide useful information because they identify large tumors or hepatic metastases. Appropriate operative planning can therefore be done. Intraoperative ultrasonography identified non-visible and non-palpable tumors in four patients, but missed one tumor in the distal tail in the hilum of the spleen. Therefore, intraoperative ultrasonography appears to influence the success of the surgical treatment of patients with insulinoma, as reported by others.[15,16] Ultrasonography probably also decreases the need for "blind" distal pancreatectomy.

Our success rate at initial reoperation was only 55% (five out of nine) and at subsequent reoperation 80% (four out of five). The main reasons for failures were a) islet cell cancer or metastatic disease (four patients), b) nesidioblastosis/hyperplasia (four patients), c) multiple neoplasms (two patients), and d) missed solitary adenomas (three patients). Some of these patients had more than one reason for failure.

Insulinomas associated with MEN 1 syndrome in many respects differ from insulinomas in patients with sporadic hyperinsulinism.[17,18] In patients with MEN 1, multiple islet cell tumors are scattered throughout the pancreas. The median number of tumors among our seven patients with multiple tumors and MEN 1 was seven. The tumors tended to vary in size, ranging in size from microscopic to 3 cm. Consequently, detection of all the tumors was difficult either by localization studies or intraoperative palpation. Fifty-five percent (six out of eleven) of the failed operations were performed on patients with MEN 1, which comprise only 16% of our patient cohort. Three of these patients also had malignant islet cell tumors. Three of the failures occurred after the initial operation and three after subsequent or reoperation. We and others have previously reported that subtotal pancreatic resection with enucleation of tumors from the head of the pancreas is necessary to avoid unsuccessful operations or recurrence.[17–20] Among the entire group of 56 patients treated surgically, hyperinsulinism has recurred or persisted in six of the twelve patients who had subtotal pancreatectomy, in one patient with distal pancreatectomy and in one patient who had a benign tumor enucleated. We and others believe that intraoperative

ultrasonography in combination with careful palpation provides the best results, thus deeming pre-operative localization studies unnecessary until better studies are developed. [13,14,18]

Intraoperative ultrasonography added to our operative success rate in four patients with nonpalpable tumors. In accordance with our findings, there are numerous publications that have recorded cases of nonpalpable tumors, which could be detected only with the help of the intraoperative ultrasonography.[21-23] In patients with MEN 1, subtotal pancreatectomy rather than enucleation is the treatment of choice because of the high probability of multiple islet cell tumors.[17,19,20] The operative failure in adults with nesidioblastosis or hyperplasia can be reduced by histological analysis of a pancreatic biopsy during the operation when no discrete tumor can be identified. If the histological analysis is confirmed, a subtotal pancreatectomy should be considered. Enucleation gave the lowest complication rate of 35% as compared to 60% and 80% complication rates for initial partial and subtotal pancreatectomies, respectively. Our mortality rate of 3% (one who died of progressive metastatic disease), and our complication rate of 43% was comparable with the 20%to 43% complication rates reported in other patient series.[18,24] Even though the fewest complications occurred after enucleation, pancreatic resections are indicated for patients with malignant insulinoma, MEN 1 and/or multiple tumors, and for large tumors in the tail of the pancreas. The complication rate and diabetes mellitus are higher for patients requiring reoperation; therefore, every effort should be made to localize and remove the islet cell tumor or tumors during the initial surgical procedure.[25]

When no tumor can be identified during the operative procedure, we favor either obtaining pancreatic vein sampling for insulin analysis or a distal pancreatectomy to diagnose patients with nesidioblastosis and hyperplasia.

REFERENCES

1. Moss NH, Rhoads JE. Hyperinsulinism and islet cell tumors of the pancreas. In: Howland JM, Jordan GL, editors. Surgical diseases of the pancreas. Philadelphia: Lippincott; 1960, p 321

2. Howard JM, Moss NH, Rhoads JE. Hyperinsulinism and islet cell tumors of the pancreas. Surg Gynecol Obstet 1950; 90:417–55

3.Wilder RM, Allan FN, Power MH, Robertson HE. Carcinoma of the islands of the pancreas, hyperinsulinism hypoglycemia. JAMA 1927; 89:348

4. Whipple AO, Frautz VK. Adenomas of islet cells with hyperinsulinism: a review. Ann Surg 1935; 101:1299–1335

5. Howland G, Campbell WR, Maltby EJ, Robinson WL. Dysinsulinism:convulsions and coma due to islet cell tumor of the pancreas, with operation and cure. JAMA 1929; 93:674

6. Perry RR, Vinik AI. Clinical Review 72:Diagnosis and management of functioning islet cell tumors. J of Clin Endoc Metab 1995; 80(8):2273–2278

7. Delcore R, Friesen JR. Gastrointestinal neuroendocrine tumors. J Am Coll Surg 1994; 178:187–211.

8. Edis AS, McIlrath DC, van Heerden JA, Fulton RE, Sheedy PF, Service FJ, Dale AS. Insulinoma—current diagnosis and surgical management. Curr Prob Surg 1976; 13(10): 1–45

9. Conn JW, Pek S. On spontaneous hypoglycemia. Current Concepts. Kalamazoo (Mich): . The Upjohn Company, 1970

10. Shatney CH, Grage TB. Diagnostic and surgical aspects of insulinoma: a review of twenty -seven cases. Ann J Surg 1974; 127:174

11.Filipi CJ, Higgins GA. Diagnosis and management of insulinoma. Ann J Surg 1973; 125:231

12. Laroche GP, Ferris DO, Priestley JT, Scholtz DA, Dockerty MB. Hyperinsulinism. Arch Surg 1968; 96: 763

13. Grant CS, van Heerden MB, Charboneau WJ, James ME, Reading CC. Insulinoma. The value of intraoperative ultrasonography. Arch Surg 1988;123:843–848

14. Dagget PR, Goodburn EA, Kurts AB, Le Quesne L P, Morris DV, Nabarro JD, Raphael MJ. Is preoperative localization of insulinomas necessary? Lancet 1981; 1(8218):483–486

15. Norton JA, Shawker TH, Doppman JL, Miller DL, Fraker DL, Cromack DT. Localization and surgical treatment of occult insulinomas. Ann Surg 1990; 212(5):615–620

16. Owens LV, Huth JF, Cance WG. Insulinoma: pitfalls in preoperative localization. Eur J Surg Onc 1995; 21(3): 326–328

17. Demeure MJ, Klonoff DC, Karam JH, Duh QY, Clark OH. Insulinomas associated with multiple endocrine neoplasia type I: the need for a different surgical approach. Surg 1991; 110(6): 998–1005

18. Van Heerden JA, Grant CS, Czako PF, Service FS, Charboneau JW. Occult functioning insulinomas: Which localizing studies are indicated? Surg 1992; 112:1010–1014.

19. O'Riordain DS, O'Brien MS, van Heerden JA, Service FS, Greant CS. Surgical management of insulinomas associated with multiple endocrine neoplasia type I. World J of Surg 1994; 18(4):488–194

20. Rasbach DA, van Heerden JV, Telander RL, Grant CS, Carney AS. Surgical management of hyperinsulinism in the Multiple Endocrine Neoplasia Type I syndrome. Arch Surg 1990; 120(3): 584–589

21. Angelini L, Bezzi M, Tucci G, Lirici MM, Candiani F, Rubaltelli L. The ultrasonic detection of insulinomas during surgical exploration of pancrease. World J Surg 1987; 11: 642–649

22. Bottger T, Schafer W, Beyer J, Junginger T. Is preoperative localization diagnostic in organic hyperinsulinism necessary or not?— A National Review.Dig Surg 1991; 8:220

23. Gorman B, Charboneau JW, James EM, Reading CC, Galiber AK, Grant CS. Benign pancreatic insulinoma: preoperative and postoperative sonographic localization. AJR 1986; 147:929.

24. Lo CY, Lam KY, Kung AW, Lam KS, Tung PH, Fan ST. Pancreatic insulinomas. Arch Surg 1997; 132(8):926–930

25. Thompson GB, Service JF, van Heerden JA, Carney AS, Charboneau W, O'Brien PC, Grant CS. Reoperative insulinomas, 1927 to 1992. An institutional experience. Surg 1993; 114(6):1196–1206

Articles

Fundamentals—Rudolf Virchow and Modern Medicine

DAVID M. REESE, MD, *Los Angeles, California*

The 19th century pathologist Rudolf Virchow was a physician, scientist, and revolutionary. The preeminent medical investigator of his day, Virchow remains best-known for his theory of cellular pathology, which laid the conceptual foundation for modern scientific medicine. Less appreciated are Virchow's numerous accomplishments in public health, anthropology, and European politics, including his quest for social justice and democracy in Imperial Germany. The study of Virchow's life and writings may provide contemporary physicians with a powerful role model as we grapple with the complexities of the modern medical enterprise.

(Reese DM. Fundamentals:Rudolf Virchow and Modern Medicine. West J Med 1998; 169:105-108)

Few physicians have the privilege of making a discovery that lays bare the workings of the body or alters the foundations of a field. For every Harvey or Osler, tens of thousands of us labor quietly in patient care or research, hoping to improve the lives of our patients or add a few bricks to the edifice of medical knowledge. Likewise, most doctors will never enter the political arena or engage in public political discourse. Certainly rare is the individual who achieves both scientific and political greatness. The nineteenth-century Prussian physician and statesman Rudolf Virchow was such a man.

Most contemporary doctors are familiar at least with Virchow's name. Many know that he was a pathologist, active in describing and cataloging the pathologic anatomy of numerous diseases. Some may remember a couple of the numerous clinical signs he described, such as the association between gastric cancer and the presence of an enlarged left supraclavicular lymph node. But few doctors are aware that the enterprise of modern scientific medicine owes more to Rudolf Virchow and his research program than perhaps any other physician, and virtually none has knowledge of his significant accomplishments in public health, politics, and social engineering.

Why should clinicians practicing medicine in the last years of the 20th century care about Rudolf Virchow? Virchow, a paragon of the accomplished researcher, the humanistic physician, and the social activist, provides a useful role model for physicians in our society. In an era in which many patients lament the fact that their doctor may be more technician and businessman than advisor and confidant, study of Virchow and his accomplishments can reinvigorate our faith in scientific medicine and its ultimate goal of alleviating human suffering.

The Physician as Scientist

Virchow was born in 1821 in northeastern Prussia near the border with Poland, an area that has oscillated between a German and Polish identity for centuries depending on whose military is ascendant. The son of a Pomeranian farmer, he received a typical primary education at the local community school and was the head of his class at the gymnasium (high school), where his ambition and love of hard work already were becoming apparent.[1,2] After completing secondary-school education, Virchow became a student at the Friedrich-Wilhelm Institut, a division of the University of Berlin dedicated to training medical officers for the Prussian army. In spite of the grinding schedule of lectures, laboratories, and studying, he developed wide-ranging intellectual interests, including philosophy, history, archaeology, languages, and politics. Driven by a vague but powerful urge to acquire "no less than a universal knowledge of nature from Godhead to stone," Virchow was rapidly becoming a polymath, that rare individual of great and diversified learning.[3]

After graduation from medical school, Virchow accepted a position as an intern at one of Berlin's famous teaching hospitals, the Charité, where he quickly developed an interest in the work of its pathologist, Robert Froriep. Froriep taught him the fundamentals of microscopy and informed him on Europe's latest medical research, acquainting the young doctor with current theories about the causes and treatment of disease.[1] Virchow's ability to read multiple European languages as well as Latin and Greek was an advantage since the scientific journals of the day were not predominantly published in one language as they are now.

From the Division of Hematology-Oncology, University of California, Los Angeles, School of Medicine.
Reprint requests to David M. Reese, MD, Urologic Oncology, 5th Floor, UCSF/Mount Zion Cancer Center, 2356 Sutter Street, San Francisco, CA 94143.

In the early part of Virchow's career, there were many theories, or so-called systems, of disease.[3] Rooted in a Romantic philosophy that claimed the scientist could uncover the truth about nature by reasoning from first principles, these medical theories were usually little more than armchair hypotheses based on incorrect or nonexistent data.[4] Each system was typically championed by one of the leading European physicians and his followers, and the medical literature of the day abounded with theoretical discourses regarding the strengths and weaknesses of the various theories. Overthrowing such theoretical systems and replacing them with scientific medicine based on observation and experiment became Virchow's stated goal.

While Virchow had great respect for clinical medicine, it was in the autospy room and laboratory that he excelled, and his research career was quickly launched. Within a few years after graduating from medical school he had made major discoveries about the processes of thrombosis and embolism.[5] In addition, he described leukemia as cancer of the white blood cells and differentiated it from pyemia, or leukocytosis.[1,5] He recognized the consequences of stopping blood flow to an organ or tissue and coined the term "ischemia" to denote this process, thus initiating the first serious research into understanding the physiologic mechanisms underlying heart attack and stroke.[6,7] Usually, Virchow conveyed his results in an argumentative and biting style that humiliated and enraged many of his staid European colleagues.

After a few years, Virchow assumed Froriep's position at the Charité. With his new professional and financial freedom he established a journal, *The Archive of Pathological Anatomy and Physiology, and Clinical Medicine*. The title itself is a direct statement about Virchow's beliefs regarding scientific medicine.[5] Virchow maintained that the way to make advances in patient care is to understand the disturbed anatomy that results from disease and, crucially, to elucidate how this change affects the function of tissues and organs. While we accept this approach as fundamental, the notion that physicians should evaluate their hypotheses by assessing the results in patients was a controversial proposition in 19th century Europe.

In the first issue of *The Archive*, Virchow published an article which was direct in approach, revolutionary in content, and specifically crafted to challenge his peers. In this paper he laid out a formal plan for medical progress based on understanding pathologic anatomy and physiology, and his exposition is worth quoting:

> Let us not deceive ourselves about the present state of medicine. It is undeniable that our spirits are exhausted by the innumerable hypothetical systems which are constantly being cast to the winds and replaced by new ones. A few more mishaps, however, and this time of disturbance will have passed by and it will be understood that only dispassionate, diligent, and steady work, true work of observation or experiment, has permanent value. The science of pathologic physiology will then gradually fulfill its promise, not as the creation of a few overheated heads, but from the cooperation of many painstaking investigators— a pathologic physiology which will be the stronghold of scientific medicine.[8]

The study of pathophysiology was to form the heart of Virchow's research program, and, moreover, this study was to be based on careful clinical observation coupled with intelligent experimentation. The modern paradigm for medical research, this method is one that has yielded steady progress against disease in the 20th century. The success of Virchow's approach can be judged also by the longevity of his journal, which after 150 years remains a respected scientific forum now known as *Virchow's Archive*.

Publishing original scientific manifestos is exemplary, but actually carrying out the research is the challenge. Virchow was more than equal to the task and spent half a dozen years doing groundbreaking work in Würzburg, where he was forced to move in 1849 after taking an active role in the failed democratic revolution of the previous year (for more on this episode, see below.) Virchow's Würzburg research accomplishments were diverse, encompassing areas such as infectious disease, cancer, derangements of the liver and kidney, and mental retardation.[2,4] The power of his scientific approach became clear as one puzzle after another fell to his method.

By the 1850s Virchow had become the preeminent physician-scientist in Europe, and in recognition of his accomplishments he finally was offered a professorship at the University of Berlin, his alma mater. Upon assuming the Chair of Pathology at the world's leading school of medicine, Virchow was about to make his most important contribution to medical science: the idea that cells are the fundamental units constituting all tissues and organs, and that disease in the organism results when cells fail to perform their normal, specialized functions. The concept of cells as the building blocks of the organism and the locus of disease may seem self-evident to modern physicians and scientists, but it was revolutionary in mid-19th century Europe. When cells are recognized as the essential components of life, no place remains for theories of disease relying on notions of evil humors, strange fluxes, disturbed animisms, or other supernatural explanations of illness.

Building on the work of various German embryologists and microscopic anatomists, Virchow had slowly developed his ideas about cells and disease while in Würzburg.[9] After his arrival in Berlin, he decided to enlighten the professors and students at the university regarding the latest developments in medical science. Virchow's series of lectures explicating the cellular theory, which were meant to be understandable to anyone with basic medical training, were issued as a book, *Cellular Pathology*. Like Newton's *Principia* two centuries earlier, the work caused an immediate sensation in Europe. Theories about disease now could be unified under a single rubric, the concept of the cell and its normal and pathologic functioning. Before Virchow, doctors could catalog the signs and symptoms of illness, observe its natural history, and describe the appearance of organs and tissues after death, but they had no coherent explanation for the fundamental cause of disease. After the

publication of *Cellular Pathology*, medical scientists had a new paradigm to use in attacking the problems of pathophysiology. Not only did Virchow's cellular pathology rid medicine of the mysterious, his work defined the principles by which physicians should seek to find the where's, why's, and how's of disease. Harvey Cushing, in his biography of William Osler, noted that Virchow's cellular doctrine set the stage for the microbiologic discoveries of Koch and Pasteur and the practical adaptation of them to surgery by Lister.[10] Cancer, viewed since ancient times as some sort of invading scourge, now could be attacked as a disease of deranged host cells.[1] In short, the modern cellular approach to biomedical research is a lineal descendant of Virchow's theory.

Politician and Humanist

Cellular Pathology prompted a revolution in medical thinking, much as the publication of Darwin's *Origin of Species* one year later heralded a paradigm shift in biology. Virchow's notion of cells as the locus of disease is clearly as important an organizing principle in medicine as evolution is in biology. Unlike Darwin, however, Virchow could boast of myriad accomplishments outside of science. He was political revolutionary, statesman, and public health advocate as well as pathologist.

Virchow's first significant political experience came in 1848, when he was still on staff at the Royal Charité in Berlin. In response to public outcry regarding a typhus epidemic raging among textile workers in Upper Silesia, the Prussian government organized a commission of investigation with Virchow as its medical officer. Appalled at the misery he encountered among peasants in the countryside, Virchow concluded that poor sanitation, ignorance of basic hygiene, lack of education, and near-starvation were the root problems of the epidemic. He issued a scathing report, lambasting the Prussian aristocracy for maintaining its subjects in a state of backwardness. As an expression of his burgeoning political liberalism, Virchow also publicly demanded "full and unlimited democracy" coupled with "education, freedom, and prosperity."[2] His inflammatory comments set the stage for direct conflict with the Prussian government.

That conflict was not long in coming. In 1848 social upheaval spread throughout Europe as revolutionaries in one capital after another took to the streets to demand freedom and democracy.[11] Berlin was no exception, and in March, a few weeks after his Silesian expedition, Virchow manned the barricades beside fellow democrats, armed with a rusty sword and an antiquated rifle.[12] He also was elected representative to a newly formed Prussian diet and delivered fiery speeches denouncing the Hohenzollerns, the royal family. When the monarchists rallied and crushed the rebellion a few months later throughout Europe, the authorities could not abide Virchow's continued presence in Berlin. He was dismissed as prosector at the Charité early in 1849 and accepted a position in Würzburg after much prodding of the local Bavarian bureaucracy.[4]

When finally lured back to Berlin in the late 1850s, Virchow quickly reentered the political realm. He was elected Berlin City Councillor in 1859, an office in which he served for 42 years. He worked tirelessly to improve the welfare of Berliners, his achievements ranging from improving the city's sewer and water supply systems to reforming the arrangement of public hospitals. In its lengthy obituary in 1902, the *British Medical Journal* opined that the fact that Berlin then ranked as one of the most hygienic cities in Europe was due almost entirely to Virchow's efforts.[13]

Virchow also was active in German national politics. A founding member of the German Progressive Party, he was elected to the House of Deputies, the lower chamber of the Prussian legislature, where he became a strenuous liberal opponent of Bismarck. As chairman of the finance committee, Virchow once blocked the creation of a German navy, which so incensed Bismarck that he challenged the pathologist to a duel. The enterprise was abandoned as ridiculous when Virchow insisted it be fought with his weapon of choice—the scalpel.7 Disturbed by the increasingly authoritarian nature of Imperial Germany, Virchow continued to agitate for democracy, separation of church and state, and social welfare programs until his retirement from active politics.[4]

Whether engaged in medical research or national politics, Virchow always was guided by a deep sense of humanitarianism. In his view the physician was a citizen uniquely equipped to further the public good, and the practice of medicine could not be divorced from its social milieu. He worked tirelessly to reform the Berlin hospital system so that all citizens would have access to adequate medical care. In the Franco-Prussian war, Virchow served as a medical officer at the front and organized the military hospital system; he insisted that all injured combatants, regardless of nationality, be entitled to medical aid. Virchow's sentiments regarding the practical aims of medicine are perhaps best summarized in an inscription he wrote on a portrait of himself: "The progress of medicine should be as the progress of humanity, the measure of its practical and theoretical utility should serve at the same time as a measure of the correctness of what it accomplishes."[14] Osler, who, as a student, had spent time in Berlin learning the art of the autopsy from the master, devoted an address to Virchow's accomplishments on the occasion of the pathologist's 70th birthday.[15] Osler believed that Virchow's scientific achievements were amplified by his consistent humanitarianism.

Lessons for Postmodernists

So what lessons can the contemporary physician draw from the life of this 19th century German pathologist? Virchow's writings remind us that medicine must be founded on science, the linking of careful clinical observation and laboratory investigation. While the tenets of scientific medicine may be unquestioned by the vast majority of us, we must remember that the scientific approach has dominated the healing arts for only a brief

time in the history of medicine. In an age of multiple alternative therapies, many based on wishful thinking or motivated by simple greed, we must remain defenders of the principles first enunciated by Virchow. We must insist that all treatments be subject to appropriate investigation.

Virchow teaches us also that medicine cannot be removed from a social context. Currently, more than 40 million Americans lack adequate health insurance, a situation that Virchow undoubtedly would have found deplorable. The majority of us genuinely lament this lack as well, but what form of political action have we effectively used to change the system? The example of the German physician is worth pondering as we grapple with the momentous changes medicine is going through at the moment.

Above all, Virchow reminds us that the essence of medicine is humanitarianism. Advocating for patients with the administrators of managed care conglomerates may not be as heroic as debating Bismarck on the floors of the Reichstag, and most of us will never achieve public renown. However, as George Eliot so perceptively observed in the last sentence of her great Victorian novel *Middlemarch*, published when Virchow was at the height of his career, "the growing good of the world is partly dependent on unhistoric acts; and that things are not so ill with you and me as they might have been, is half owing to the number who lived faithfully a hidden life, and rest in unvisited tombs."[16]

Acknowledgments

I am indebted to Ackernecht[2] and Boyd[4] for general biographical data. I also thank Dr. Gary Schiller for helpful suggestions on the manuscript.

REFERENCES

1. Winter K: Virchow. Leipzig/Jena: Urania-Verlag; 1956
2. Ackernecht EH: Rudolf Virchow: doctor, statesman, anthropologist. Madison (WI): Wisconsin Press; 1953
3. Rather LJ: Rudolf Virchow and scientific medicine. Arch Int Med 1957; 100:1007-1014
4. Boyd BA: Rudolf Virchow: the scientist as citizen. New York: Garland; 1991
5. Nuland SB: Doctors: the biography of medicine. New York: Alfred A. Knopf; 1988
6. Schiller F: Concepts of stroke before and after Virchow. Med Hist 1970; 14:115-131
7. Nuland SB: How we die. New York: Vintage Books; 1993
8. Virchow R. Translation quoted in Nuland SB: Doctors: the biography of medicine. New York: Alfred A. Knopf; 1988, p 313
9. Rather LJ: Rudolf Virchow's views on pathology, pathological anatomy, and cellular pathology. Arch Path 1966; 82:197-204
10. Cushing H: The life of Sir William Osler. London: Oxford University Press; 1940
11. Hobsbawm H: The age of revolution. London: Weidenfeld & Nicolson; 1962
12. Gardner LI: Doctors afield – Rudolf Virchow. New Engl J Med 1955; 252:587-589
13. Rudolf Virchow [obituary]. Br Med J 1902 Sep 13:795-800
14. Semon F, Rudolf Virchow: some personal reminiscences. Br Med J 1902 Sep 13:800-802
15. Osler W: Rudolf Virchow: man and student. Boston Med Surg J 1891; 125:425-427
16. Eliot G. Middlemarch. New York: Modern Library edition; 1994

Epitomes

Important Advances in Clinical Medicine

Urology

Daniel A. Nachtsheim, MD, Section Editor

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in urology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, as to both scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in urology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Urology of the California Medical Association, and the summaries were prepared under the direction of Dr Nachtsheim and the Panel.

Best Screening Tests for Prostate Cancer

In 1998 alone, about 500 men will be diagnosed with prostate cancer every day, and approximately 39,000 will die of the disease. Recognizing that population screening for prostate cancer using PSA and DRE have neither been proven or disproven to be effective to reduce the morbidity and mortality of the disease, authorities now recommend that physicians and health care organizations provide the pros and cons and let the well-informed patient decide. Just as it would be wrong to mandate screening, it would be just as wrong to not offer the option of early detection tests for prostate cancer.

Potential screening tests for prostate cancer include the digital rectal exam (DRE), the seromarkers prostate specific antigen (PSA) and prostatic acid phosphatase (PAP), and transrectal ultrasound of the prostate (TRUS). The DRE remains an important method of detecting many prostate cancers that may be missed with a PSA test. The PSA test is a simple blood test. Although PSA and PAP are both seromarkers for prostate cancer, the latter is inappropriate for use in screening because levels of PAP often do not become elevated until the disease has reached an advanced stage. Therefore, PAP should be used only for staging the disease after it has been diagnosed and never for screening. Transrectal ultrasound of the prostate is not a suitable screening test. It cannot differentiate many small cancers from surrounding non-cancerous prostate tissue, but it is appropriate for directing biopsies in men who have abnormal findings on DRE or PSA testing.

The PSA test has been approved by the US Food and Drug Administration as a method of screening for prostate cancer, but it is not perfect. Although a PSA level > 4.0 ng/ml is considered abnormal, men with a level of between 4.1 and 10.0 ng/ml, often considered the "grey zone," will have prostate cancer detected about one-third of the time. In men with a PSA level >10.0 ng/ml, approximately two-thirds will have cancer. The specificity is only 59% for all PSA levels >4.0 ng/ml. Sensitivity is also suboptimal, as levels >4.0 ng/ml will detect prostate cancer in only 79% of cases. In other words, the use of this cutoff point will miss 21% of patients with prostate cancer who have PSA levels of <4.0 ng/ml.

Several recent refinements may improve the clinical utility of PSA. Measurements of PSA density are based on the ratio between the PSA level and the prostate volume (as measured on transrectal ultrasound). A PSA density value less than 0.15 in a patient suggests that benign prostatic hypertrophy (BPH) alone may be responsible for the PSA elevation and a biopsy may not be indicated if the digital rectal examination is normal. This method helps adjust for the proportion of PSA elevation that may be related simply to BPH. However, the reliability of the method depends on reproducible measurements of prostate volume by transrectal ultrasound.

Assessments of PSA rate of change or PSA velocity are useful for men who undergo screening over a period of time. A PSA increase >0.75–0.80 ng/ml over a one-year period may indicate an increased probability of prostate cancer and may signal the need for further evaluation. On the other hand, recent research has suggested that men who start with a very low PSA value less than 2.0 ng/ml have a very low probability of jumping to a worrisome PSA over one year and that every-other-year testing may be acceptable for this group. Some, but not all studies have suggested that digital rectal examination, ejaculation, or bicycle riding may raise the PSA level unrelated to prostate cancer leading to a false positive test. In a man with mildly elevated PSA level, these things should be avoided for 48–72 hours prior to repeat testing.

Recently, the use of age-specific reference ranges (ASRRs) has generated particular interest. These ranges,

derived from control populations of men without prostate cancer, adjust for the increases in prostatic hyperplasia and PSA levels that occur with aging. Levels above the 95th percentile of these normal men by decade of age are considered abnormal. Newer data have suggested that different racial groups may have different ASRRs. For instance, ASRRs are lower in Japanese men than in American men. Also, African American men with newly diagnosed prostate cancer have higher serum PSA values than do whites, even after correction for stage, grade, and tumor volume.

Aside from PSA-density, rate-of-change and ASRR, another tool—the "free" PSA—has recently been FDA-approved. Over the last few years, researchers discovered that PSA protein may be free or bound to other proteins in the bloodstream. Most PSA is complexed to other proteins, most commonly a protein called alpha-1 antichymoltrypsin (ACT). The percentage of free, complexed and total PSA and their ratios are different between men who do and do not have prostate cancer and these differences can be exploited to screen for prostate cancer. The most useful ratio identified to date is the percentage of free PSA to the total PSA. Although studies are still being conducted, it appears that the lower the percent of free PSA, the higher the risk of prostate cancer.

With the aging of the U.S. population and the high incidence of prostate cancer, the debate regarding the early detection of the disease continues. Although randomized clinical trials have yet to prove or disprove the efficacy of prostate cancer population-based screening, patients should be counseled regarding the pros and cons of early detection. The PSA and DRE tests are accepted case finding tools. Many urologists favor a strategy of annual PSA blood tests and DREs for men >50 years old. Annual assessments should begin at age 40 for African American men and those who have a family history of prostate cancer. New "PSA-tools" such as age- and race-specific reference ranges and free-PSA seem to make the testing more reliable. The relationships between testing, treatment, and outcome need further clarification.

JUDD W. MOUL, MD
Bethesda, Maryland

REFERENCES

US Preventive Services Task Force. Screening for prostate cancer. In: Guide to clinical preventive services. 2nd ed. Baltimore, MD: Williams and Wilkins; 1996, pp 119–134Presti, JC, Hovey, R, Bhargava, V, Carroll, PR, Shinohara, K. Prospective evaluation of prostate specific antigen and prostate specific antigen density in the detection of carcinoma of the prostate: ethnic variations. J Urol 1997; 157:907–912

Carter, HB, Epstein, JI, Chan, DW, Fozard, JL, Pearson, JD. Recommended prostate- specific antigen testing intervals for the detection of curable prostate cancer. JAMA 1997; 277:1456–1460

Catalona, WJ, Smith, DS, Ornstein, DK. Prostate cancer detection in men with serum PSA concentrations of 2.6 to 4.0 ng/ml and benign prostate examination. JAMA 1997; 277:1452–1455

Morgan TO, Jacobson SJ, McCarthy WF, et al. Age-specific reference ranges for prostate-specific antigen in black men. N Engl J Med 1996; 335:304-310

Urolithiasis

RENAL AND URETERAL stones are frequently encountered In industrialized countries, in contrast to bladder calculi noted in developing countries and ancient times. Most ureteral calculi are passed spontaneously. Extracorporeal shock wave lithotripsy (ESWL), ureteroscopy, and percutaneous nephrolithotomy are saved for patients in whom spontaneous passage has failed. Dietary modifications and medical treatment can reduce recurrent urinary stone disease substantially. Despite improved surgical treatment, 50% of patients will have recurrent stones within 5 years if no metabolic intervention is undertaken.

Patients usually present with acute flank pain associated with nausea and vomiting. Chronic back pain, hematuria and incidental discovery with radiographic imaging are other frequent reasons for referral to urinary stone centers. Eighty-five percent of patients with urinary calculi will have either micro or gross hematuria. A complete blood count is warranted for patients who have calculi and fever. Serum electrolytes and creatinine should be obtained. A plain abdominal radiograph (KUB) is the best initial imaging modality; it helps pinpoint the location of the calculus, since 85-90% of urinary tract calculi are radio-opaque. The KUB may be followed by directed renal sonography or intravenous pyelography to confirm stone location and guide management. Where available, non-contrast helical CT scanning is becoming the examination of choice for acute renal colic. It is safe, rapid, and has shown 97% sensitivity and 96% specificity in detecting renal and ureteral calculi.

Acute renal colic is treated initially with analgesics and hydration to maintain a euvolemic state. The majority of ureteral calculi less than 6 mm in size will pass with this management. Pain, persistent vomiting, fever, or failure of stone progression requires intervention.

A medical evaluation for patients who form stones more than once should be initiated after the acute stone episode is resolved. The stone should be retrieved and analyzed. Serum electrolytes, creatinine, calcium, phosphate, uric acid, and parathyroid hormone (PTH) should be obtained. A 24-hour urine collection including urine volume, pH, specific gravity, calcium, creatinine, citrate, oxalate, phosphate, uric acid, and sodium will direct medical therapy.

Stone analysis, revealing either calcium or non-calcium calculi, guides medical management. Most stones are composed of calcium oxalate. Pure calcium phosphate calculi may indicate the presence of distal renal tubular acidosis (RTA) or primary hyperparathyroidism. Hypokalemia and decreased serum bicarbonate with a fasting urinary pH > 5.5 confirms the diagnosis of distal RTA (type1). Elevated serum PTH, calcium and decreased serum phosphorus characterize patients with primary hyperparathyroidism.

Calcium urolithiasis can be subdivided into hypercalciuric and normocalciuric states. The hypercalciuric metabolic defects may be sub-classified as absorptive, resorptive and "renal leak".

There are 3 classes of absorptive hypercalciuria: diet independent (type I), diet dependent (type II), and renal phosphate leak (type III). All are characterized by >250 mg. of calcium in a 24 hour urine specimen. Type I

patients have elevated urine calcium during both high and low calcium intake. Serum calcium and PTH are normal. Thiazide diuretics or cellulose phosphate are effective treatments and decrease urinary calcium excretion. Type II hypercalciurics exhibit hypercalciuria only during increased calcium dietary intake. Therapy is directed at decreasing dietary calcium by about 50% to approximately 400 mg/day; over the long term bone density is stable. Type III absorptive hypercalciuria is secondary to a renal phosphate "leak". The low serum phosphate stimulates vitamin D and subsequent absorption of phosphate and calcium. Treatment with bioavailable phosphate (neutral orthophosphate) is effective.

Resorptive hypercalciuria is due to primary hyperparathyroidism and is treated with surgical removal of the parathyroid adenoma.

Renal "leak" hypercalciuria is caused by defective tubular reabsorption of calcium. Secondary hyperparathyroidism is often noted. This condition is successfully treated over the long term with thiazides.

Hyperuricosuria, hypocitraturia and hyperoxaluria comprise the normocalciuric conditions associated with calcium lithiasis. Hyperuricosuria may be associated with gout, myeloproliferative states and malignancy but is most frequently due to dietary overindulgence. Monosodium urate crystals act as nidi for calcium oxalate stones by heterogeneous nucleation. Decreased sodium intake is critical for management, as with hypercalciuric states. If reduced intake of dietary purines is unsuccessful, allopurinol is usually effective.

Hyperoxaluria is most commonly due to chronic diarrheal states such as inflammatory bowel disease. Increased fecal fats bind to intraluminal calcium, thus calcium is unavailable to bind to oxalate which is readily absorbed. Mild cases may be controlled with intake of calcium rich foods with meals to bind dietary oxalates. More severe cases may require calcium containing antacids at mealtime.

Citrate is a potent inhibitor of calcium lithiasis, acting by complexing with urinary calcium in solution. Low urinary citrate (<320 mg/day) is associated with conditions resulting in a metabolic acidosis (i.e., chronic thiazide use, renal tubular acidosis, diarrhea). These patients are successfully treated with citrate supplements, such as potassium citrate or naturally occurring citrate found in lemonade.

The three most common non-calcium stones are uric acid, struvite, and cystine. Less common stones may be matrix, xanthine, or drug related (triamterene and indinavir).

Uric acid calculi are relatively radiolucent and patients consistently have urinary pH <5.5. The stones may be dissolved with urinary alkalinization (oral KCitrate or K bicarbonate) at a rate of 0.5 cm per month. Solubility of uric acid rapidly rises above pH 6.0. As with all stone formers, patients should be encouraged to maintain a urinary output of 1.5-2.0 liters per day. They are encouraged to drink fluid with meals, 2 hours after each meal, and prior to bedtime, adequate enough to awaken the patient to void.

Struvite stones (magnesium ammonium phosphate) occur in the presence of infection with urea-splitting organisms and are most commonly seen in women. They frequently present with non- E. coli recurrent urinary tract infections. Sterilization of the calculi using antibiotics is futile; surgical removal of the infected stones remains the cornerstone of treatment. A full metabolic evaluation is necessary because most stones are of mixed composition and metabolic defects may be identified.

Cystinuria is a hereditary defect affecting the transport of dibasic amino acids in the small bowel and renal tubules. Elevated levels of urinary cystine precipitate at normal urinary pH (5.8-6.0); the solubility of cystine increases above pH 7.5. Treatment centers on urinary alkalization, hydration and sulfhydryl binding agents such as alpha mercaptopropionyl glycine (Thiola).

Urinary stone disease is common and is usually characterized by acute onset of severe colic. Stone size does not correlate with the severity of symptoms. Frequently, small ureteral stones are most painful. Although recurrences often mark the course of this disease, dietary manipulation and medical therapies can result in stone prevention and avoidance of complications.

NOAH S. SCHENKMAN, MD
MARSHALL L. STOLLER, MD
San Francisco, California

REFERENCES

Levy FL, Adams-Huet B, Pak CY. Ambulatory evaluation of nephrolithiasis: an update of a 1980 protocol. Amer J Med 1995; 98:50-59

McDonald MW, Stoller ML. Urinary stone disease: a practical guide to metabolic evaluation. Geriatrics 1997; 52:38-40, 49-52, 55-56

Baggio B, Plebani M, Gambaro G. Pathogenesis of idiopathic calcium nephrolithiasis: update 1997. Critical Reviews in Clinical Laboratory Sciences 1998; 35:153-187

Epidemiology of Prostate Cancer

IN 1996 ALONE, 317,000 men were diagnosed with carcinoma of the prostate. The overall incidence.showed a slight rise in 1989 followed by a sharp rise in 1991, peaking in 1992–93. Since then, there has been a gradual decline. The observed increase is a response to an aggressive nationwide prostate screening program.

It has long been known that the incidence of prostate cancer increases with age. Of major significance and interest now are the varying rates of incidence of prostate cancer according to racial distribution. The incidence is highest among African-Americans at 188 per 100,000 person-years, intermediate among whites at 139 per 100,000 person-years and lowest among Asians at 39 per 100,000 person-years for Japanese and 28 per 100,000 person-years for Chinese. Of significance is the observation that Asians living in the United States have a higher incidence of prostate cancer than those residing in their country of origin, but still lower than whites and African-Americans.

In addition to a higher incidence, it appears that African-American men with prostate cancer have a higher grade and larger cancer volume when compared to Caucasian men. They may also have a significantly higher prostate specific antigen (PSA) level after radical prostatectomy, suggesting a greater residual tumor bur-

den. Some feel that these data argue for aggressive and early detection programs among African-American men, although the outcome of treatment is still being evaluated.

Family history of prostate cancer is now a recognized risk factor for prostate cancer.The relative risk for a man developing it depends on the number of affected relatives (about 1.4 with one affected first degree relative and over 3 with more than one.) Current data suggest that familial prostate cancer may be a more aggressive type of cancer. Patients with familial prostate cancer have a worse outcome after radical prostatectomy than patients with nonfamilial prostate cancer. The poor result is primarily related to a higher distant relapse rate, suggesting that familial cancer is biologically more aggressive. Recent reports confirm the existence of a rare autosomal dominant prostate cancer susceptibility gene dubbed "HPC1" for "hereditary prostate cancer 1." Some feel these data argue for aggressive early screening for men with family history of prostate cancer, although outcome studies have not been completed.

In addition to the racial and familial risk factors associated with prostate cancer, several other risk factors are being hotly pursued, but are not established. Factors being evaluated include cigarette smoking and.consumption of dietary fat, tomatoes, and supplemental selenium. Other areas of interest include association with farming and history of vasectomy.

As cigarette smoking is implicated with lung cancer, it is also being investigated for its relationship with prostate cancer. Higher death rates from prostate cancer in current cigarette smokers suggesting that smoking may adversely affect survival in prostate cancer patients, however.

Dietary factors have been correlated with prostate cancer. Early studies support the hypothesis that high dietary fat intake is correlated with prostate cancer. Dietary fat intake was observed primarily with animal fat and meat consumption rather than vegetable fat consumption. Recent reports, however, tend to refute the previously asserted association, finding no link between dietary fat, especially animal sources, with risk or mortality of prostate cancer. Epidemiologic studies suggest high consumption of tomatoes or supplemental selenium may protect against prostate cancer. These findings need confirmation before dietary changes are made.

Recent reports indicate a positive correlation between prostate cancer and farming. Authors are speculate that hormonally active agricultural chemicals are potential risk factors among farmers.

The suggestion that vasectomy may increase the risk of prostate cancer is being disputed by evaluating confounding factors. For example, the odds ratio estimate for prostate cancer associated with vasectomy tended to increase among men with such known risk factors as father and brother with prostate cancer. Any increased risk may be related to detection bias or differential participation rates due to both vasectomy status and a family history of prostate cancer.

ANANIAS C. DIOKNO, MD
Royal Oak, Michigan

REFERENCES

Schaid DJ, Thibodeau SN, Blute ML, McDonnell SK. Genetic epidemiology of prostate cancer. J Urol 1997; 157(Suppl):53

Rodriguez C, Heath CW, Jr, Calle EE, Thun MJ, Tatham LM. Smoking and fatal prostate cancer in a large cohort of adult men. Am J Epidemiol 1997; 145:466–75

Veierod MB, Thelle DS, Laake P. Dietary fat intake and risk of prostate cancer: a prospective study of 25,708 Norwegian men. Int J Cancer 1997; 73:634–8

Clark LC, Dalkin BL, Krongrad A, Witherington R, Herlong JH, Carpenter HD. Decreased incidence of prostate cancer with selenium supplementation. J Urol 1997; 157 (Suppl):56 [Au: Please list up to 6 authors, then use et al.]

Keller-Byrne JE, Schaub EA, Khuder SA. Meta-analyses of prostate cancer and farming. Am J Ind Med 1997; 31:580–6

Zhu K, Weiss NS, Brawer MK, Stergachis A, McKnight B, Daling JR, Stanford JL.Vasectomy and prostate cancer: a case-controlled study in a health maintenance organization. Am J Epidemiol 1996; 144:717–22

Sildenafil: A Milestone in the Treatment of Impotence

With an estimated 18–30 million American men who experience some degree of erectile dysfunction, it is not surprising that sildenafil, the first effective oral treament agent, released under the trade name Viagra by Pfizer Co. in April 1998, has been the fastest selling drug in pharmaceutical history. Sildenafil is an inhibitor of phosphodiesterase type 5 (PDE5). When initially investigated in patients with cardiac disease to promote vasodilatation, many reported improved erectile response.

Erections occur through sexual stimulation of the parasympathetic nervous system leading to release of the neurotransmitter nitric oxide, a powerful vasodilator derived from the endothelial cells lining the penile spaces—the corpus cavernosum. Nitric oxide then produces cyclic GMP which causes the smooth muscle of the corpus cavernosum to relax and fill with arterial blood, creating the erection. Pressure from these expanding spaces occludes veins against the tunica albugenia, surrounding the erectile tissue and leading to sustained erection.

Sildenafil works by blocking the enzyme, phosphodiesterase 5, which breaks down cyclic GMP, leading to higher sustained levels of cyclic GMP and relaxation of the smooth muscle spaces of the penis, and thereby amplifies sexual stimulation. Sildenafil has no direct effect on increasing libido but may enhance the sexual experience by decreasing performance anxiety caused by anticipated failure.

Available in 25, 50, and 100 milligram tablets,(a 50 mg tablet is the most common dose), sildenafil is taken about one hour prior to sexual activity to allow for absorption. Effects last 3–5 hours. About 70% of men with erectile dysfunction experience improved erections. Most side effects are attributable to vasodilatation: headache and flushing(10%). Additionally, about 3% of patients experience mild and transient visual effects—predominantly color tinge, but also light sensitivity—a pharmacological response thought to be related to sildenafil's weak inhibition of PDE6, found in the retina. The most serious side effect is hypotension, which may be amplified by concomitant use of nitrates, therefore, use with nitroglycerin or other nitrates is contradicted. Deaths reported to date in patients taking sildenafil do not appear to be greater than the same cohort

of cardiac patients not taking the drug. The Federal Drug Administration is investigating all reported deaths.

Sildenafil is not present in significant amounts in the ejaculate and it therefore poses no risk to conception or pregnancy in women whose partners take the drug.

Although with sildenafil oral pharmacotherapy becomes the front line treatment in the "goal-orientated" approach to to treatment, underlying medical conditions such as hypogondism, diabetes mellitus, and hypertension also need to be addressed in men with impotence.

What about women? Early reports suggest that sildenafil can increase lubrication and vascular vaginal engorgement in women, but safety and efficacy have not been established and sildenafil is not currently recommended for use in women. Several studies are underway, however.

Other drugs expected to be available shortly include phentol amine mesulate (Vaso-MaxTM by Zonagon Corp.), an apha-blocker reported to be effective in 40% of men by increasing penile arterial blood flow. In addition, a refined form of apomorphine delivered by sublingual administration will be available. Apomorphine does not affect cyclic GMP, but rather acts as a dopamine agonist, modulating erections through the nervous system. Early reports suggest a 50% effectiveness rate. Finally, research efforts will inevitably produce other phosphodiesterase inhibitors similar to sildenafil.

What about penile injections and the other forms of impotence treatment? The proven success of penile injection pharmacotherapy with agents such as prostaglandin E, and combinations as "tri-mix" (prostaglandin, papaverine and phentolamine) remains durable, and makes this approach still reasonable and cost effective. A difference in the mechanism of action of the injectables from sildenafil allows for success of these agents where sildenafil may fail. Intra-urethral insertion of prostaglandin E pellets (M.U.S.E by Vivus corp) remains an option for 10-20% of men. Yohimbine hydrochloride tablets (Yocon), 5.4 mg 3 times a day, are effective for 5–15 % of men.

Mechanical devices remain available in the form of the vacuum erection device and the surgically inserted penile prosthesis. It is currently unclear whether sildenafil will be an enhancement to these mechanical aids.

If medications, mechanical devices, or counseling are not effective, then referral to a urologist is appropriate.

DANIEL NACHTSHEIM, MD
La Jolla, California

REFERENCES

1. Boolell, M., Gepi-Attee S, Gingell JC, Allen MJ. Silenafil: a novel effective oral therapy for erectile dysfunction. Br J Urol 1996; 78: 257-261

2. Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker, PA. Oral sildenafil in the treatment of erectile dysfunction. N Engl J Med 1998; 338:1397–1404

ADVISORY PANEL TO THE SECTION ON UROLOGY

RAYMOND FAY, MD
Advisory Panel Chair
CMA Council on Scientific Affairs Representative
San Francisco

DANIEL A. NACHTSHEIM, MD
CMA Section Chair
La Jolla

DANIEL A. NACHTSHEIM, MD
CMA Section Secretary
La Jolla

HARRY NEUWIRTH, MD
CMA Section Assistant Secretary
Greenbrae

HERBERT RUCKLE, MD
Loma Linda University

HARCHARAN S. GILL, MD
Stanford University

RALPH W. DEVERE WHITE, MD
University of California, Davis

THOMAS E. AHLERING, MD
University of California, Irvine

RICHARD M. EHRLICH, MD
University of California, Los Angeles

JOSEPH D. SCHMIDT, MD
University of California, San Diego

PETER R. CARROLL, MD
University of California, San Francisco

STUART BOYD, MD
University of Southern California

RAYMOND FAY, MD
California Urological Association
San Francisco

HARRY NEUWIRTH, MD
Northern California Urological Society
Greenbrae

PHILLIP WISE, MD
San Diego Urological Society
La Jolla

DAVID W. RHODES, MD
Los Angeles Urological Society
Pasadena

ASHOK J. KAR, MD
Orange County Urological Society
Santa Ana

KATHY A. DESANTIS
Invited Guest
Santa Ana

KATHRYN DUKE, JD, MPH
CMA Staff
San Francisco

LESLIE BIRNBAUM
CMA Staff
San Francisco

Alerts, Notices, and Case Reports

Chronic Lymphocytic Leukemia in a Patient With Sickle Cell Anemia

HYUN SUE KIM, MD
LISA YOSPUR, MD
YUTAKA NIIHARA, MD
Torrance, California

REPORTS OF HEMATOLOGIC MALIGNANCIES in patients with sickle cell anemia are rare—only two cases (Hodgkin's disease and acute myeloblastic leukemia) before 1960.[1,2] Since then, significant improvement has been made in supportive care of sickle cell anemia patients (such as early institution of antibiotics in suspected infections), and more hematological malignancies have been reported, including acute lymphoblastic leukemia, chronic granulocytic leukemia, multiple myeloma, malignant histiocytosis, non-Hodgkin's lymphoma, and cutaneous T cell lymphoma.[3–19] To our knowledge, this is the first report of chronic lymphocytic leukemia in a patient with sickle cell anemia.

Report of a Case

In April 1992, a 56-year-old African-American man with a history of sickle cell anemia presented at Harbor-UCLA Medical Center. The results of hemoglobin electrophoresis were consistent with homozygous S sickle cell anemia in both cellulose acetate and citrate gel, and his white blood cell count was 30,700/μL with 52% lymphocytes, hematocrit 28.1%, reticulocyte count 16% (corrected 9.9%), and platelet count 234,000/μL. In December of that year, he was admitted to Harbor-UCLA Medical Center because of acute hyperkalemia (serum potassium 8.5 mmol/L). His medical history also included chronic active hepatitis B and C, probably acquired through blood transfusion for management of his sickle cell anemia.

During the patient's hospitalization in December, the Hematology Service was consulted when his white blood cell count was found to be elevated (71,300/μL). Physical examination revealed bilateral inguinal lymphadenopathy and hepatomegaly (10 cm below the right costal margin), but the spleen was not palpable. Hematocrit was 15.6% and platelet count 230,000/μL. There was mild elevation of liver enzymes (aspartate aminotransferase 65 mU/mL and alanine aminotransferase 28 mU/mL). A peripheral blood smear demonstrated lymphocytosis consisting of small mature lymphocytes, smudge cells, and sickle cells (Figure 1), and a bone marrow biopsy showed hypercellular bone marrow with erythroid hyperplasia and focal lymphocytosis, prompting the diagnosis of CLL (Figure 2). The patient was discharged after hemodialysis brought his serum potassium from 8.5 mmol/L to the normal range (3.3–5.4 mmol/L). His hyperkalemia was thought to be secondary to type IV renal tubular acidosis.

In January 1993, the patient's white blood cell count increased to 94,900/μL with 88% lymphocytes; his hematocrit was 14.7% and his platelet count 336,000/μL. He was referred for local radiation therapy (30 Gy over 4 weeks to bilateral inguinal lymph nodes). The inguinal lymphadenopathy resolved, his white blood cell count decreased to 35,500/μL, his hematocrit was 17.5%, and his platelet count was 208,000/μL. His hematocrit remained lower than usual for sickle cell anemia, and his serum erythropoietin level was also found to be inappropriately low (133 units/L), so in September 1994, he was started on erythropoietin injections. His hematocrit increased to 19–21%.

Between January 1993 and July 1995, the patient's white blood cell count gradually increased to 300,000/μL. The patient received chemotherapy with fludarabine at 25 mg/m^2/day for 5 days in July 1995, preceded by intravenous immunoglobulin (400 mg/kg) to aid his immune function. After treatment, a decrease in hematocrit to 11% necessitated a red cell transfusion of two units. After just one cycle of therapy, the patient appeared clinically stable for approximately 3 months—by September 1995, his white cell count was 7,900/μL. With progression of the chronic active hepatitis, however, his liver began to fail. In March 1996, at age 60, he died of fulminant liver failure.

Discussion

Because hematologic malignancies in patients with sickle cell anemia have been rare, some authors have hypothesized that the abnormal red blood cell has a protective role against malignancies.[20] A simpler explanation might be that patients with sickle cell anemia have a short life expectancy. In 1973, the estimated median survival of U.S. patients with sickle cell anemia was reported to be 14 years from diagnosis, most dying before the age of 40.[21] Data reported in 1995 indicate that median survival has increased to 42 years for men and 48 years for women.[22] Steinberg and colleagues[23] reported five patients with sickle cell anemia who survived into their eighth decade (their ages ranged from 71 to 76 years at the time of the report). They were not unaffected by their disease, however, and serious complications became apparent in later

(Kim HS, Yospur L, Niihara Y: Chronic Lymphocytic Leukemia in a patient with sickle cell anemia. West J Med 1998; 169:114-116)

From the departments of Medicine (Drs Kim and Niihara) and Pathology (Dr Yospur), Harbor-UCLA Medical Center, UCLA School of Medicine, Torrance, California.

Reprint requests to Yutaka Niihara, MD, Department of Medicine, Division of Hematology, C-1, Room 12, Harbor-UCLA Medical Center, 1124 W Carson St, Torrance, CA 90502-2064.

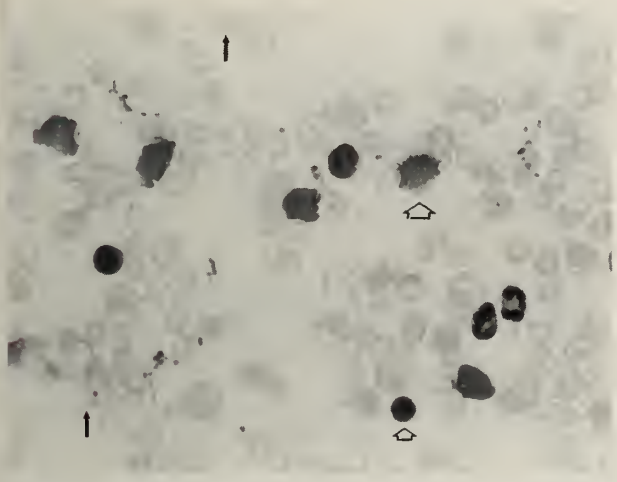


Figure 1.—Photomicrograph of a peripheral blood smear demonstrates sickle cells (▼), Howell-Jolly bodies (➡), and numerous hypochromic-microcytic cells. Notice the scattered "smudge" cells (⇨) and small mature lymphocytes (⇨). Modified Wright-Giemsa, ×400.

TABLE 1.—*Reported Hematologic Malignancies in Sickle Cell Anemia Since 1960*

Malignancy	*No. of Patients*	*Reference*
Acute myelogenous leukemia	4	2–6
Non-Hodgkin's lymphoma*	4	7, 10, 14, 19
Acute lymphoblastic leukemia	3	3, 15, 18
Chronic myelogenous leukemia	3	8, 9, 16
Hodgkin's disease	3	1, 7, 11
Multiple myeloma	3	12, 13, 17
Malignant histiocytosis	1	7
Chronic lymphocytic leukemia	1	Present case

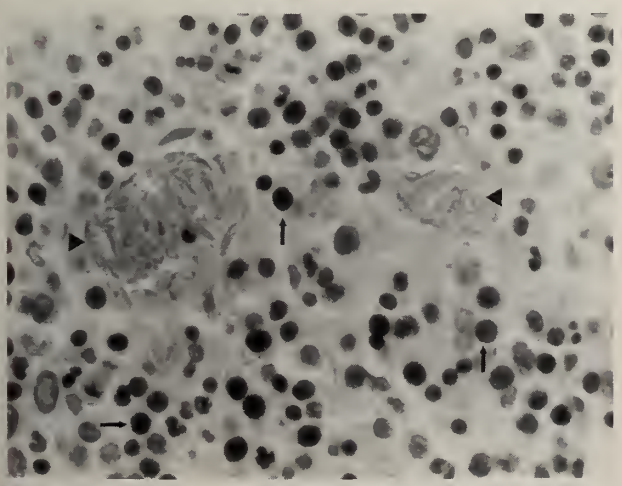
*Included a case of cutaneous T cell lymphoma.

years.[23] Similarly, the hematologic malignancies common to older patients are seen more often as sickle cell anemia patients age.

Our patient most likely had at least Rai stage 2 CLL as evidenced by hepatomegaly. With chronic active hepatitis, the size of the liver is not likely to be enlarged to the degree seen in this patient without significant elevation of liver enzymes. As of April 1992 his liver enzymes were not significantly elevated. Therefore, it is likely that the cause of his hepatomegaly was CLL rather than chronic active hepatitis. In stage 2 CLL, splenomegaly may also be expected, but it will not be found in an adult patient with sickle cell anemia due to infarctions earlier in life. It is difficult to determine stage 3 disease when a patient has underlying anemia, and this patient's baseline anemia may have been compromised further by chronic liver disease.

Of the reported cases of hematological malignancies in sickle cell anemia (Table 1), ours is the only case of CLL. In retrospect, the CLL diagnosis should have been made in April 1992, when his white blood cell count was 30,900/μL with 52% lymphocytes, but the underlying leukocytosis of sickle cell anemia may have delayed the diagnosis.

Underlying anemia also limited treatment options. In January 1993, to minimize bone marrow suppression, local radiation therapy was chosen rather than chemotherapy. Radiotherapy resolved the symptomatic lymphadenopathy and reduced the lymphocyte count without the complications of systemic chemotherapy (e.g., severe transfusion-dependent anemia or thrombocytopenia, infections from neutropenia).



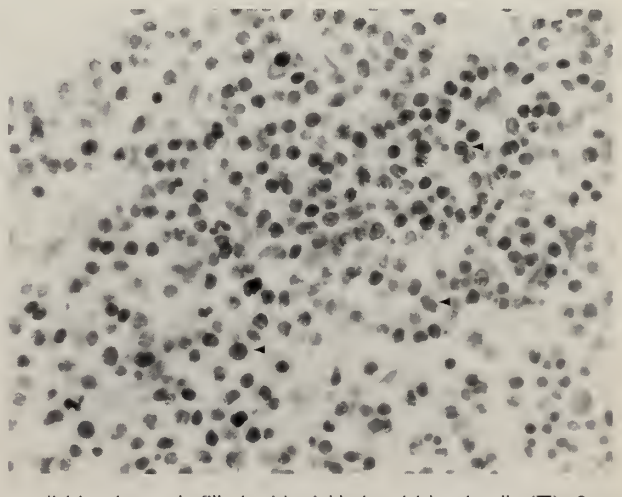


Figure 2.—A: Photomicrograph of a bone marrow biopsy depicts small blood vessels filled with sickled red blood cells (▼). Surrounding the vessels is an exuberant erythrocytic hyperplasia with numerous erythroblasts (➡). Hematoxylin and eosin, (600. B: Focal aggregates of lymphocytes (▼) are noted within the bone marrow biopsy with an overall increase of up to 50% of nonerythroid nucleated cells. Hematoxylin and eosin, ×400.

Later, when systemic chemotherapy was considered, we again had to proceed cautiously. We gave prophylactic gamma globulin just before chemotherapy in an attempt to prevent infectious complications (this patient was already immunosuppressed due to asplenia and CLL). His hematocrit was extremely low at 15 to 17%.

He responded moderately to erythropoietin (prechemotherapy hematocrit ~20%). Even so, he required a transfusion of packed red blood cells when his hematocrit rapidly dropped to 11% shortly after the chemotherapy. Ideally, we would have liked to prevent such a extreme drop in hematocrit. Frequent monitoring of blood count and clinical status cannot be overemphasized. The response of the CLL was excellent, however, and with aggressive monitoring and supportive care, the patient tolerated the therapy.

Acknowledgments

The authors would like to thank Drs Kouichi R Tanaka and Nora CJ Sun for their helpful advice.

REFERENCES

1. Kato K, Cardozo WW. Hodgkin's disease with terminal eosinophilia occurring in a negro child with sicklemia. J Pediatr 1938; 12:165–175

2. Goldin AG, Kelty KC, Beard MF. Sickle cell anemia terminating in acute myeloblastic leukemia. Ann Intern Med 1953; 39:920–926

3. Jackson RE, Short BJ. Frequency and prognosis of coexisting sickle cell disease and acute leukemia in children. Clin Pediatr 1972; 11:183–185

4. Samal GC. Sickle cell anemia with acute myeloid leukemia. A case report. Indian Pediatr 1979; 16:453–454

5. Johnson FL, Look AT, Gokerman J, Ruggiero MR, Dalla-Pozza L, Billings FT. Bone marrow transplantation in a patient with sickle cell anemia. N Engl J Med 1984; 311:780–783

6. Clinicopathologic Conference. Left elbow pain and death in a young woman with sickle cell anemia. Am J Med 1982; 73:268–282

7. Stricker RB, Linker CA, Crowley TJ, Embury SH. Hematologic malignancy in sickle cell disease: report of four cases and review of literature. Am J Hematol 1986; 21:223–230

8. Nowell PC, Jensen J, Gardner F. Two complex translocations in chronic granulocytic leukemia involving chromosomes 22, 9, and a third chromosome. Hum Genet 197; 530:13–21

9. Phillips Jr G, Hartman J, Kinney TR, Sokal JE, Kaufman RE. Chronic granulocytic leukemia in a patient with sickle cell anemia. Am J Med 1988; 85:567–569

10. Williams AO. Haemoglobin genotypes, ABO blood groups, and Burkitt's tumour. J Med Genet 1966; 3:177–179

11. Salmassi S, Currie ET, Bolf EC, Hernandez M, Kasprisin DO. Hodgkin's disease in a patient with sickle cell anemia. Cancer 1981; 48:252–254

12. Anderson IS, Yeung KY, Hillman D, Lessin LS. Multiple myeloma in a patient with sickle cell anemia. Am J Med 1975; 59:568–574

13. Talerman A, Serjeant GR, Milner PF. Normal pregnancy in a patient with multiple myeloma and sickle cell anemia. West Indian Med J 1971; 20:97–100

14. Fishman SJ, Rietschel RL, Cooper ES, McBurney E. Photopheresis in coexistent cutaneous T cell lymphoma and sickle cell disease. J Am Acad Dermatol 1991; 25:331–332

15. Bigner SH, Friedman HS, Kinney TR, Kurtzberg J, Chaffee S, Becton D, Falletta JM. 9p– in a girl with acute lymphocytic leukemia and sickle cell disease. Cancer Genet Cytogenet 1986; 21:267–269

16. Sarma PSA, Chawda BK, Das SR. Chronic myelocytic leukemia in a patient with sickle cell anemia. J Assoc Physicians India 1986; 34:821–822

17. Sarma PSA, Viswanathan KA, Mukherjee MM. Multiple myeloma in a patient with sickle cell anemia. J Assoc Physicians India 1986; 34:877–878

18. Njoku OS, Johnson SB, Kulkarni AG, Mba EC. Acute lymphoblastic leukemia in a Nigerian adult with sickle cell anemia. Central African J Med 1988; 34:158–160

19. Morabito F, Callea V, Brugiatelli M, D'Ascola D, Palazzolo A, Neri A. Non-Hodgkin's lymphoma associated with sickle cell disease: a case report. Tumori 1987; 73:523–524

20. Pandit HM. Potential use of globins and their derivatives of abnormal red blood cells in the treatment of cancer and related immune disorders. Med Hypotheses 1993; 40:332–334

21. Diggs LM. Anatomic lesion in sickle cell disease. In Abramson H, Bertles JF, Wethers EL (Eds): Sickle Cell Disease: Diagnosis, Management, Education, and Research. St. Louis, MO: C.V. Mosby, 1973, pp 189–229

22. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, Klug PP. Mortality in sickle cell disease: life expectancy and risk factors for early death. N Engl J Med 1994; 330:1639–1644

23. Steinberg MH, Ballas SK, Brunson CY, Bookchin R. Sickle cell anemia in septuagenarians (letter). Blood 1995; 86:3997–3998

Suppurative Parotitis

DONALD C. SHEPPARD, MD
HENRY F. CHAMBERS
San Francisco, California

SUPPURATIVE PAROTITIS, an uncommon condition of the elderly and severely ill, is often associated with dehydration and sialolithiasis.[1,2] We report an unusual case featuring a mixed infection of *Candida albicans* and *Streptococcus pyogenes* and review the history and management of suppurative parotitis.

Report of a Case

A 19-year-old man had a 3-week history of polyuria and polydipsia and a 3-day history of fever and right-sided facial swelling and pain. His medical history was unremarkable except for a left parotid duct stone without parotitis, which was treated conservatively when he was 5 years old. Upon physical examination, he was dehydrated, his breath had a fruity odor, and his right parotid gland was swollen, tender, and erythematous. No discharge from Stensen's duct was noted. Facial nerve function was normal bilaterally throughout the clinical course. Laboratory results showed a total white blood cell count of 17×10^9/L, blood glucose 1529 mg/dL, positive serum ketones, and arterial pH 7.11; HIV serology was negative.

The patient was given intravenous fluids and insulin, and therapy was begun with oral amoxicillin/clavulanate for presumed parotitis. After 48 hours, his ketoacidosis and hyperglycemia had resolved, but he still had a fever and a swollen parotid gland. Amoxicillin/clavulanate was discontinued and intravenous nafcillin therapy begun. The next day, a computed tomography (CT) scan revealed intraparotid fluid collection. Purulent material (10 cc) was drained through an operative incision; staining of the fluid revealed few gram-positive cocci and moderate budding yeast in chains, and the cultures subsequently grew both *Candida albicans* (heavy) and *Streptococcus pyogenes* (moderate). Antibiotic therapy was changed to intravenous cefuroxime.

(Sheppard DC, Chambers HF:Suppurative parotitis. West J Med 1998;169:116-117)

From the Medical Service, San Francisco General Hospital, Department of Medicine, University of California San Francisco.

Reprint requests to Dr HF Chambers, Box 0811, Division of Infectious Diseases, San Francisco General Hospital, University of California San Francisco School of Medicine, 3rd and Parnassus Avenues, San Francisco, CA 94143.

After 72 hours of cefuroxime, the patient remained febrile with persistent swelling and erythema of the parotid incision. A second CT scan failed to demonstrate any fluid collection and, in view of the culture results, therapy with intravenous amphotericin B was begun. Within 48 hours, the patient's fever, swelling, and erythema resolved.

Etiology and Presentation

Acute suppurative parotitis affects predominantly the elderly and severely ill. In a 1962 study,[2] 131 of 161 patients developed parotitis in the context of severe or multiple diseases. Most patients were more than 60 years of age; 43% were older than 70. Common predisposing features were preexisting oral disease (77%), dehydration (50%), malnutrition (68%), and the use of medications that reduce oral secretions (25%).[2]

Given the correlation of dehydration and antisialogogues with parotitis, one mechanism of parotitis may be retrograde transductal migration of oral microorganisms in the context of either decreased salivary flow or partial obstruction by a sialolith.[2] Underlying oral disease predisposes to changes in mucosal flora, as does bacterial overgrowth of the oral cavity, which has been documented in states of impaired salivation. The altered oral flora contribute to infection as mucosal surfaces are colonized by microorganisms with enhanced pathogenicity. This model—change in oral flora with subsequent ascending infection—fits well with the isolation of *Candida* species in our patient. It may be that oropharyngeal candidiasis associated with uncontrolled diabetes3 and decreased salivary flow associated with the dehydration of ketoacidosis provide the factors necessary for the development of parotitis.

Staphylococcus aureus is the most common pathogen isolated in suppurative parotitis; alpha hemolytic streptococci and enteric gram-negative rods have been documented in a minority of cases. In 1961, Krippaehne et al. noted that of 66 parotid glands, 41 contained staphylococci alone; 20 contained both streptococci and staphylocci; eight contained gram-negative bacteria; and two contained pneumococci.[2] In contrast, a recent study using modern anaerobic culture techniques[4] found that of 36 isolates from patients with suppurative parotitis, 20 contained anaerobic bacteria and only 16 contained the traditional pathogens of staphylococci, streptococci, or gram-negative bacilli. The anaerobes isolated were predominantly oral anaerobic organisms such as *Peptostreptococcus sp.* and *Fusobacterium sp.*;[4] unusual cases of parotitis with *Treponema pallidum, Mycobacterium sp., Eikenella sp.*, and *Bartonella sp.* have been documented.[1] Fungal parotitis in the context of diabetes has also been reported in an elderly woman who developed a parotid abscess with *Torulopsis glabrata*.[5]

Suppurative parotitis presents relatively acutely with the onset of unilateral swelling, erythema, and tenderness of the parotid gland. Fever, leukocytosis, and other signs of systemic illness are common. Intraorally, the parotid duct is often visible and edematous, and it may have a purulent discharge at the orifice. Abscess formation is common and clinically difficult to distinguish from simple parotitis, as the dense parotid capsule prevents extension of purulence to the skin. Complications, both systemic and local, are common. Bacteremia and subsequent systemic sepsis with multisystem organ failure and death have been reported.[2] Locally advanced disease can penetrate anteriorly to the skin and soft tissues of the face, inferiorly to the planes of deep tissue in the neck where abscess formation and septic thrombophlebitis of the jugular vein can occur, or posteriorly to the mandible, temporomandibular joint, or middle ear and external auditory canal. Facial nerve palsy may result, both as a consequence of the local infection and as a complication of surgical interventions.

Management

Medical therapy alone is usually succesful in suppurative parotitis; surgery is reserved to manage local complications and failures of medical management. The series of Krippaehne[2] recorded the need for surgical intervention in 47 of 161 cases, usually after a trial of medical therapy. Before antibiotic therapy is begun, the clinician should obtain adequate culture material, including any drainage from Stensen's duct, to guide organism-specific therapy. Fine-needle or surgical aspiration may be required to obtain an adequate sample, which is cultured for aerobic bacteria, anaerobic bacteria, and fungus infection. Initial therapy is directed at staphlococci and streptococci and then modified according to the culture results and response to therapy.[1] Suitable regimens include intravenous nafcillin and oral dicloxacillin; clindamycin is an alternative for the patient allergic to penicillin. In the event of suboptimal clinical response to therapy, imaging studies such as CT or sonography may identify the presence of a parotid abscess, which mandates early and aggressive drainage. In the absence of such a focal collection, a more exhaustive microbiological search is appropriate.

REFERENCES

1. Brook I. Diagnosis and management of parotitis. Arch Otolaryngol Head Neck Surg 1992; 118:469–471

2. Krippaehne WW, Hunt TK, Dunphy JE. Acute suppurative parotitis: a study of 161 cases. Ann Surg 1962; 156:251–257

3. Zegarelli D. Fungal infections of the oral cavity. Otolaryngol Clin North Am 1993; 26:1069–1089

4. Brook I, Frazier EH, Thompson DH. Aerobic and anaerobic microbiology of acute suppurative parotitis. Laryngoscope 1991; 101:170–172

5. Pujol F, Angirekula M, Weiner M, Jindrak K, Pachter BR. Parotitis due to *Torulopsis glabrata*. Clin Infect Dis 1995; 21:1342–1343

Commentary

Society and Public Health: Crisis and Rebirth

JONATHAN M. MANN, MD, MPH, *Philadelphia, Pennsylvania*

This paper was presented at the Institute of Medicine Annual Meeting in Washington, DC, on October 20, 1997.

Nearly a decade ago, the Institute of Medicine (IOM) declared public health to be in "disarray." Today, disarray has deepened into a crisis of identity about the nature, roles, and responsibilities of public health.

The mission of public health was elegantly defined in the 1988 IOM report, as "[assuring] the conditions in which people can be healthy." The crisis in public health can be summarized in two questions. What do we know about these essential conditions for health? How we define the conditions determines what we do about them. Second, what are we doing about them? Put bluntly, public health knows enough to act, but does not. The reasons for this disconnectedness suggest what will be required for a creative renewal, a renaissance of modern public health.

In discussing the conditions in which people can achieve health—that is, physical, mental, and social well-being—there is frequently tension, even dichotomization, between so-called "individual factors" and "societal factors." The latter term usually refers to factors largely, if not entirely, beyond the control of the individual. To illustrate, consider—*ourselves*! To what extent is our well–being, including professional achievement, exclusively a result of our personal character traits? On the other hand, to what extent have we been supported, promoted, and advanced by circumstances and other forces? Dag Hammerskjold, former (UN) Secretary-General, recognized this when he wrote that being born in Scandinavia was like getting a winning ticket in the lottery of life. Clearly, the societal context weighs heavily. A child born in an inner city does not have the same life chances nor, predictably, the same health status as a child born in a middle-class suburb.

Consider that while obesity is increasingly common in America, there are few obese students at Harvard College, or in medical schools. Unless body habitus predicts intelligence, other factors and influences must be invoked to explain this disparity. We see societal influence in countries where a woman does not refuse unwanted or unprotected sexual intercourse not because of ignorance about pregnancy or risks of AIDS, but from fear of being beaten without judicial recourse, or being divorced, the equivalent of civil and economic death for the woman.

The core of public health knowledge is not only that a blend of individual and societal factors are involved in determining health and associated behaviors like diet, exercise, tobacco smoking, drug and alcohol use, and sexual behavior. Rather, for many, if not most, people, the societal context weighs heavily, if not overwhelmingly, as a determinant of health status. Yet paradoxically, public health has avoided addressing directly the societal conditions which largely determine the burden of preventable disease, disability, and premature death.

This socio-paresis of public health—this reluctance and inability to work directly on the societal roots of health problems—has several sources. First, much societal-level research has focused on socioeconomic status, an amalgam of educational attainment, income, and job prestige, and the results show that higher socioeconomic status powerfully predicts longer and healthier life. Yet while everyone may agree that poverty is the problem, what should be done? The poverty diagnosis is remarkably paralyzing of specific and concrete action by public health.

Thus, for example, teenage pregnancy, sexually transmitted infections, and injection-drug use are linked closely to the socioeconomic gradient. Yet, unable or unwilling to supersede pointing to societal issues like stifled educational or economic opportunity, public health often engages in hollow blaming exercises. "Decision-makers" and a "lack of political will" are targeted. Public health retreats, working to reduce collateral damage by providing health education, counseling, contraceptives, and treatment. This approach, though humane and useful, is inadequate, for it fails to address underlying sources of vulnerability to health problems.

Another source of public health paralysis is the pervasive American belief in the transforming capacity of individual character. This focus on the individual in public health is almost unconsciously abetted by traditional epidemiologic methodology, which predetermines that risk factors and behaviors generally will be identified at

(Mann JM. Society and Public Health: Crisis and Rebirth. West J Med 1998; 169:118–121)

From the School of Public Health, Allegheny University of the Health Sciences, Philadelphia, PA.
Reprint requests to Jonathan M. Mann, MD, MPH, 1505 Race Street, Bellet Building, 11th Floor, Mail Stop 660, Philadephia, PA 19102.

an individual level, and by the pervasive, unspoken acceptance within public health of the individualistic health belief model and its derivatives as the dominant conceptualization of health-related behavior. Accordingly, despite knowing better, public health often targets individual behavior, isolated from societal context, in its prevention efforts.

Technology is another mechanism for avoiding societal issues. Almost subconsciously, the Holy Grail of public health becomes technology and, preferably, interventions that function without any active participation by the public. Of course, some important public health achievements—safe drinking water and sanitation, for example—work automatically once implemented, and their contribution to public health is enormous. Yet we know that even the most effective interventions of this kind, such as childhood immunization or removal of lead paint from old dwellings, cannot be separated from those nettlesome and complex societal issues that present day-to-day difficulties like getting children their immunizations, or paying for lead abatement in the inner cities. The search for public health technology can displace and even distract from efforts to resolve the real societal nature of the barriers involved. In addition, a commitment to making technological advances equitably accessible is essential.

Curiously, the multi-disciplinarity of public health is another escape mechanism from dealing with societal issues. This situation is somewhat paradoxical because the presumed purpose of drawing together diverse disciplines, including economics, political science, biomedicine, social and behavioral science, and law, is to generate a rich analysis of health status and the conditions which constrain or promote health. Yet while each discipline provides useful information, they do not cohere. Disciplines joust for pre-eminence, forming a collage rather than constituting a coherent public health analysis of health and associated societal factors. In the end, what does public health do, concretely, based on the collection of disciplinary analyses?

Finally, by drawing so close to biomedical science that research in schools of public health may be difficult to distinguish from research in medical schools, public health has sought to share the credibility, legitimacy, and resources which society accords to science in general and medicine in particular. Applying the scientific method, which is burdened by enormous assumptions and obvious and important benefits, was, at some level, an effort by public health to become or appear "value-free." Thus, public health too often studies health without intruding upon larger, societal, inescapably value-laden issues.

Not surprisingly, this pattern of avoiding the societal factor in public health leads to serious disarray, to malaise, and to a disconnectedness between what is important and where energies are placed and efforts are rewarded. For example, epidemiology, the core science of public health, seems to expend more and more time and resources in studying, with greater sophistication and precision, issues of less and less public health significance. Where is the well-funded, well-coordinated consortium of public health research that draws on all forms of relevant public health expertise and is explicitly dedicated to identifying the societal determinants and contributors to vulnerability to preventable disease, disability, and premature death in America?

Disarray also is signaled by the lack of an articulated ethics of public health. At present, there is simply not enough common ground within the field regarding its essential roles and responsibilities to be able to develop an ethics, or to explore adequately the contextual application of fundamental ethical principles to the work of public health.

Of course one could argue that given incomplete knowledge about the precise nature of societal determinants, public health inaction regarding societal issues is prudent, or appropriate. But, as the IOM report emphasized, public health is an applied activity; we cannot and must not wait until all is understood. So now we find ourselves inescapably confronted with the Gordian knot of public health: how to address directly the societal determinants of health? If the public health mission is to assure the conditions in which people can achieve the highest attainable state of physical, mental and social well-being, and if those essential conditions predominantly are societal, then public health must work for societal transformation. To proceed, three heretofore missing elements will be needed: a conceptual framework for identifying and analyzing the societal factors which constitute "the conditions in which people can be healthy," a vocabulary to speak about commonalities among health problems experienced by very different populations, and some clarity about the nature or direction of necessary societal change to address these societal conditions.

To reconnect public health with society—to catalyze a fundamental shift in how the problem is seen—important insight likely will come from outside traditional professional boundaries. Allow me to adapt slightly Newton's famous remark, "We will also be able to see beyond the present because we stand upon the shoulders of the giants who preceded us."

Largely in response to acute challenges—domestic violence, HIV/AIDS, humanitarian emergencies—a series of new, transformative insights about health and society recently have emerged. Collectively, these involve a shift away from the biomedical traditions of public health. The language of biomedicine, designed and superbly adapted for its specific purposes, hardly suffices to analyze societal issues, just as medical ethics falter when addessing macro-ethical dilemmas which involve resource distribution or environmental policies.

We need another language, with a capacity for societal analysis. In response, at first implicitly and now explicitly, public health has drawn close to human rights.

An historic and civilizational event, modern human rights is an efforts to identify, promote, and protect the societal pre-conditions for human well-being. The rights described in the key documents, starting with the 1948 Universal Declaration of Human Rights, are a series of

non-provable beliefs about the societal foundation of individual and collective well-being. Human rights frame the question of the essential societal conditions for well-being in terms of what governments should not do (such as discriminate, deny equality under law, interfere with freedom of movement or peaceful assembly, invade privacy, or deny political participation) and what governments should ensure for all (such as a basic education, social security, access to medical care, adequate housing, and food). While derived from fundamental, often unspoken, values, modern human rights achieve their status and legitimacy not from divine inspiration, but by having been developed, voted upon, and adopted by all nations and having been incorporated into the domain of international law.

Through its focus on societal determinants of well-being, human rights provides public health with a more useful framework, vocabulary, and guidance for analysis and direct response to the societal determinants of health than any framework inherited from the past biomedical or public health tradition. In addition, human rights focus on, and inevitably challenge, the status quo of society, which, in a fundamental way, is what public health also must re-learn how to do.

The health and human rights connection was recently, powerfully, and concretely applied in the domain of reproductive health and population policy. The 1994 UN Conference on Population and Development in Cairo radically redefined population programs toward a goal to ensure that women can make and effectuate free and informed choices about their reproduction. To help realize this goal, traditional public health would focus on individual decision-making by providing information, counseling, and contraceptive services. The innovation at Cairo was to go beyond traditional measures by identifying and then calling for action on the societal forces which strongly condition women's ability to make and effectuate free and informed choices regardless of access to information and contraceptive services.

Rather than analyzing societal context through the disciplinary vocabularies of economics, political science, anthropology, or sociology, societal forces were described in terms of women's human rights. Only to the extent these rights—including freedom from discrimination, the right to equality before the law, equal rights in marriage, and the right to political participation—are realized, can reproductive health and population policies approach more complete fulfillment. Rather than devaluing traditional approaches, strengthening human rights as an integral part of population policies emphasizes that without attention to the societal preconditions, defined as issues of human rights, health programs will remain inherently limited and inadequate.

Having defined the societal preconditions in this manner, public health can work directly to promote human rights through many forms of advocacy, data collection and analysis, policy development, and community organization.

Viewing the societal contribution to preventable disease, disability, and premature death through a rights perspective disaggregates the societal issue into discrete elements such as promoting the right to information, or equal rights in marriage, which are highly amenable to concrete efforts at the local or national levels. Public health can contribute both by becoming an advocate for human rights and by participating and credibly and forcefully presenting the case for protecting and promoting rights in order to protect and promote health.

The major public health problems confronting this country—violence, injuries, preventable cancer and heart disease, HIV/AIDS, alcohol, tobacco and other drug use, and obesity—are amenable to a human rights-based analysis and response. Recognition of the inextricable connection between health and human rights already is catalyzing new thinking and new forms of collaborative action.

Even beyond the synergistic contribution of a human rights dimension, the public health/human rights dialogue is stimulating a profound rethinking of the taxonomy of health. Shifting our vantage point toward the universe of human suffering, discrimination and other violations of human rights can be considered as primary pathogenic forces. For example, how much and what kinds of damage to physical, mental, and social well-being can be attributed to racism in America? To find out, rather than searching for a specific disease outcome resulting from violations of human rights, an approach analogous to the single pathogen, single disease model, it may be more appropriate to anticipate that violations of rights would increase the vulnerability to a wide range of opportunistic, adverse health events. The details of these events would then be shaped by environmental exposures and genetic or other factors.

Consider also dignity and its violation. The first article of the Universal Declaration of Human Rights puts dignity first, stating that "all human beings are born equal in dignity and rights." Enormous personal and societal energy is invested in protecting and preserving individual and collective dignity.Those of us who live in generally dignity-affirming circumstances react when our dignity is violated. Even briefly recalling such an instance evokes strong feelings of shame, humiliation, disgust, anger, and sadness. How then must well-being be affected by repeated and sustained violations! Violations of dignity are painful events fostered by disparities in perception of human worth which in turn reflect differences in social status, wealth, power, prestige, and influence. These experiences have such significant, pervasive, and long-lasting effects that injuries to individual and collective dignity may represent a hitherto unrecognized pathogenic force of destructive capacity toward human well-being at least equal to that of viruses or bacteria. In 50 years, public health may look back and wonder how we could have failed to recognize this pathogenic force. Clearly, much remains to be discovered in the world of human suffering and its alleviation.

The public health search for primordial causes inexorably leads us deep into the realm of society. The belief that re-connection of public health with society would involve, indeed require, a focus on values seems, in retro-

spect, entirely natural because renewals involve a return to sources and public health started as a social movement.

Public health knows that progress requires multiple and often simultaneous action. To the traditional approaches and to the science of public health, a new dimension of linkage with human rights and dignity is being added. While justifiably skeptical about silver bullets, whether chemical or conceptual, the inextricable link between health and human rights is not an ideology. The link is an exploration that calls for a vision of society sufficiently coherent and meaningful to anchor new creativity and energy in an effort to insure to all, the societal conditions in which their physical, mental, and social well-being can best be realized. Human rights are only ideas, but they are ideas of unusual power with the capacity to change lives and the course of history. Thus, a time of crisis in public health is also the threshold of a rebirth.Dedication to solving the most difficult issues, to societal values as well as scientific values, and to believing that the world can change joins public health to the commitment best expressed by Martin Luther King when he said that, "the moral arc of history is long, but it bends towards justice."

REFERENCES

1. Institute of Medicine. The Future of Public Health. National Academy Press, Washington, DC, 1988

2. Leaning J: Human rights and medical education. Why every medical student should learn the Universal Declaration of Human Rights. BMJ 1997; 313:1390-91

3. International Planned Parenthood Federation. IPPF Charter on sexual and reproductive rights. International Planned Parenthood Federation, London, UK, 1996

4. Mann JM: Medicine and public health, ethics and human rights. Hastings Ctr Report 1997; 27(3):6-13

INSTRUCTIONS FOR AUTHORS

In accordance with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (URM), 1997

Our readers represent all branches of medicine. We wish to receive and publish manuscripts that are reliable and lively and that will improve the care of patients, the health of the public, or policies affecting either. Manuscripts should be of interest to a broad range of scholars, busy practitioners, students, and physicians in training who have a clinical orientation. The purpose of a paper or letter may be to report, inform, alert, review, and discuss, but, above all, to teach. Titles should be short and intriguing. Avoid the overuse of jargon, adverbs, and expendable words and phrases; use only standard abbreviations and acronyms; and use inclusive language (see AMA Manual of Style, 8th Edition). We appreciate your interest in The Western Journal of Medicine and our profession.

Manuscript Information

Manuscripts should be sent to the Editor, Linda Hawes Clever, MD, c/o Publisher, The Western Journal of Medicine, 1224 West Main Street, Suite 200, Charlottesville, VA 22903-2858. Manuscripts must be original, not previously published, and not under consideration by another publisher. If preliminary data were included in another presentation or publication, this should be noted in the cover letter, and a copy of that publication should be included. Any conflict of interest, actual or potential, should be revealed to the Editors (see Letter of Transmittal). Obtaining informed consent to protect patients' rights to privacy should be documented according to URM 1997.

All manuscripts should be double-spaced and, including references and abstract but not tables, should not exceed:

- Articles: 3,000 words (15 double-spaced pages)
- Conferences and Reviews: 3,000 words
- Topics in Primary Care Medicine: 3,000 words
- Case Reports, Alerts, and Notices: 1,500 words
- Commentaries: 2,000 words
- Lessons From the Practice: 1,000 words
- Letters to the Editor: 500 words
- Epitomes: 800 words

Manuscripts, except for Case Reports, Epitomes, and Lessons From the Practice, should include a nonstructured abstract of no more than 150–200 words summarizing the article. Abstracts should include a description of the purpose, design, patients, results, and conclusions.

Letters to the Editor must be double-spaced and will be published at the discretion of the Editors. They may be edited for style and brevity. Those of a scientific nature may be subject to peer review. They should be no more than 500 words in length. Authors will be sent page proofs before publication.

All manuscripts will be subject to peer review in addition to review by the Editors to determine the originality, validity, and importance of content and conclusions. Reviewers' comments will be returned with rejected manuscripts at the discretion of the Editors. All reviewers will remain anonymous but will be required to state possible conflicts of interest.

All accepted manuscripts are subject to copyediting, and the corresponding author is sent edited page proofs for approval and necessary minor changes. Excessive changes at this stage may result in a delay of publication or withdrawal of the paper. No changes will be made after the final, edited version has been approved by the corresponding author without notifying the author. It is the corresponding author's responsibility to clear all corrections and changes with coauthors.

Letter of Transmittal

All authors must sign the letter of transmittal, with one author designated as correspondent and his or her name, address, and telephone and fax numbers included.

The order of authorship is determined by the authors. All authors should meet the basic criteria for authorship (as stated below). Because the order of authorship is assigned in different ways, its meaning cannot be inferred accurately unless it is stated by the authors. Authors may explain the order of authorship in a footnote.

A letter of transmittal, except for one accompanying a manuscript from US Government employees whose work was done as part of their official duties, must include a paragraph that transfers copyright: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns, or otherwise conveys all copyright ownership to The Western Journal of Medicine, in the event that such work is published by the journal."

The letter of transmittal must include a statement of author responsibility signed by all authors: "I have participated in the conception and design of this work and in the writing of the manuscript and take public responsibility for it. I have reviewed the final version of the manuscript and approve it for publication. I attest to the validity and legitimacy of data in the manuscript and agree to be named as the lead author or coauthor of the manuscript."

The letter of transmittal must include a description of sources of funding and the role of sponsors, including their involvement, if any, in review and approval of the manuscript for publication. The letter must also include a statement of financial disclosure: "I warrant that I have no financial interest in the drugs, devices, or procedures described in the enclosed manuscript (except as disclosed in the attached statement)."

Research or project support should be included as a footnote to the manuscript or in the accompanying cover letter.

Manuscripts concerned with experimental investigation on human subjects must include in the text a statement that all subjects gave their informed consent and that approval was obtained from the appropriate ethics committee.

Acknowledgments will be printed on a select basis—to acknowledge those who contributed to but were not involved in the writing or review of the paper. They should not include persons whose work on the manuscript was a part of their regular duties.

Preparation of Manuscripts

Everything, including references, tables, figure legends, and abstracts, must be double-spaced.

Please submit the following: The original manuscript, two copies, and a copy of the manuscript on disk (labeled with the word processing program used). Allow a margin of 2.5 to 4 cm (1 to 1.5 in) on both sides. Be sure to include the references, tables, and figure legends on the disk. Formatting should be kept to a minimum. Manuscripts transmitted by facsimile machine are not acceptable unless requested by the Editors.

All values should be in Systeme International (SI) units, with metric equivalents following in parentheses. Tempera-ture readings should be given in Celsius. Use the generic name of drugs, with the salt or ester given at the initial mention of a drug.

Figures (illustrations) should be submitted in triplicate in black and white, unmounted 12.7 X 17.8 cm (5 X 7 in) glossy prints, with the figure number, lead author's name, and top of the photo indicated with a label on the back. Patients (and relatives) have a right to anonymity in published clinical documentation. Details that might identify patients should be avoided unless essential for scientific purposes. Masking of the eye region in photographs of patients may be inadequate protection of anonymity. If identification of patients is unavoidable, informed consent should be obtained. This should be clearly stated and proof submitted with the manuscript. Changing the data on patients should not be used as a way of securing anonymity.

Figure legends, to be typed in sequence on the same page, should be in complete sentences. Any figures or tables previously published must be accompanied by a letter of permission to borrow from the copyright holder (the previous publisher). The permission of the authors should also be obtained. The Editors discourage the use of borrowed figures or tables.

Reprints

A form for ordering reprints will be sent to the corresponding author when the article is published.

References

All references should be cited in the text using superscript numbers and listed in their order of citation. They should be pertinent to the text and not simply a listing of the results of a computerized search. They should be in URM style according to the following examples. Do not use op cit or ibid.

References should be medical, scientific, or scholarly publications. Others—such as newspapers or magazines—should be kept to a minimum.

Journal Articles

Abbreviations of journal titles should conform to those used in Index Medicus. List up to six authors; for seven or more, use et al after listing the first six.

1. Vega KJ, Pina I, Krevsky B. Heart transplantation is associated with an increased risk for pancreatobiliary disease. Ann Intern Med 1996; 124:980–983
2. Parkin DM, Clayton D, Black RJ, Masuyer E, Friedl HP, Ivanov E, et al. Childhood leukaemia in Europe after Chernobyl: 5 year follow-up. Br J Cancer 1996; 73:1006–1012

No author given:

3. Cancer in South Africa [editorial]. S Afr Med J 1994; 84(12):15

Books

4. Ringsven MK, Bond D. Gerontology and leadership skills for nurses. 2nd ed. Albany (NY): Delmar Publishers; 1996 [author of book is same as author of chapter]
5. Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press; 1995, pp 465–478 [authors of book differ from chapter author]

Correspondence

6. Shusterman D. Espresso maker's wrist [correspondence]. West J Med 1990; 152:721–722

Scientific or Technical Report

Issued by funding or sponsoring agency:

7. Smith P, Golladay K. Payment for durable medical equipment billed during skilled nursing facility stays. Final report. Dallas (TX): Dept of Health and Human Services (US), Office of Evaluation and Inspections; 1994 Oct. Report No.: HHSIGOEI69200860

Issued by performing agency:

8. Field MJ, Tranquada RE, Feasley JC, editors. Health services research: work force and educational issues. Washington DC: National Academy Press; 1995. Contract No.: AHCPR282942008. Sponsored by the Agency for Health Care Policy and Research
9. Centers for Disease Control and Prevention. Recommendations and Reports: 1997 Revised guidelines for performing CD4+ T-cell determinations in persons infected with human immunodeficiency virus (HIV) MMWR 1997; 46(Jan 10):RR-2

Proceedings

10. Kimura J, Shibasaki H, editors. Recent advances in clinical neurophysiology. Proceedings of the 10th

International Congress of EMG and Clinical Neurophysiology; 1995 Oct 15–19; Kyoto, Japan. Amsterdam: Elsevier; 1996

Mass Circulation Publications

11. Lee G. Hospitalizations tied to ozone pollution: study estimates 50,000 admissions annually. The Washington Post 1996 Jun 21; Sect A:3 (col 5)

Personal Communications and Unpublished Data

The use of "personal communication" or "unpublished data" should be avoided and should not be included in the reference list. If such a notation provides essential information not available from a public source, it should be given in parentheses in the body of the text, listing the person's name, highest academic degrees, and professional affiliation, whether the communication was oral or written, and the date (month and year):
12. Lyme disease has been reported in red squirrels (J. Sneed, PhD, Department of Wildlife, written communication, September 1990).

For Further Information

Questions regarding the Instructions for Authors may be directed to the Managing Editor, Allison Spearman, 1224 W. Main St., Ste. 200, Charlottesville, VA 22903-2858. Telephone (804) 817-2000, Fax (804) 817-2020.

Additional copies of Instructions for Authors are also available through an on-demand fax request line 24 hours a day. Call (804) 817-2000 to receive a faxed copy of the Instructions for Authors.

AUTHOR CHECKLIST

- ✓ Original manuscript and 2 copies; diskette.
- ✓ Everything double-spaced.
- ✓ Illustrations, black and white glossy, identified with lead author's name—3 sets, plus figure legends that describe fully and in complete sentences what the figure depicts.
- ✓ Letter of transmittal that includes release of copyright, statement of conflict of interest, funding source(s), and authorship responsibility, signed by all the authors.
- ✓ A 200-word unstructured abstract.
- ✓ Title page that includes current affiliation of all authors and an address and telephone and fax number for corresponding author.
- ✓ Permission-to-borrow letters for any previously published illustrations or tables.
- ✓ All references numbered consecutively, double-spaced, in URM style, and cited in text. No unpublished data or nonscientific publications listed in references (include in text).
- ✓ Informed consent obtained.

Classified Advertisements

The rate for each insertion is **$1.50 per word, with a 30 word ($45) minimum.** Confidential box number charge: $10 each month.
A word is defined as one or more letters bounded by spaces. The following gives some examples:

Linda H. Clever, MD	= 4 words
Send CV	= 2 words
A	= 1 word
February 22, 1997	= 3 words
allergy/immunology	= 1 word
Sacramento, CA 95817	= 3 words
804-979-8034	= 1 word

Classified display rate $70 per inch. Maximum sizes: 1 column by 5" or 2 columns by 2" (2-1/8" per column). Larger classified ad space by special arrangements.
Copy for classified advertisements should be received not later than **first of the month preceding issue. All copy must be typed or printed.** Classified advertisers using Box Numbers forbid the disclosure of their identity; your inquiries in writing will be forwarded to Box Number advertisers. Although *The Western Journal of Medicine* believes the classified advertisements in these columns to be from reputable sources, we do not investigate the offers made and assume no liability concerning them. The right is reserved to reject, withdraw, or modify all classified advertising copy in conformity with the decisions of the Advertising Committee.

Please Type or Print Advertising Copy

Classified Advertisements Are Payable in Advance
CLASSIFIED ADVERTISEMENTS, THE WESTERN JOURNAL OF MEDICINE
2 WEST TAUNTON AVENUE, BERLIN, NJ 08009
(609) 768-9360; FAX (609) 753-0064
Ads may be placed online at www.wjmed.com

PHYSICIANS WANTED

IDAHO

Make One Of America's Best Places to Live Even Better.

Where You'll Work.
Primary Health, Idaho's largest, fastest-growing integrated health care system whose network of family medicine immediate care centers, by-appointment family practitioners, pediatricians and OB/GYNs serves beautiful southern Idaho.

Where You'll Live.
In a great place to raise a family with quality schools, incredible outdoor recreation and a rural atmosphere close to a metropolitan area with a beautiful performing arts center, excellent hospitals and professional sports.

What You'll Get.
The financial backing and medical resources of a major health care network. A competitive salary, ownership options, flexible work and call schedules, professional growth, full benefits including medical and dental and much more.

Submit CV and questions to:
BECKY NELSON
(800) 688-5008 ext. 507 • FAX (208) 344-4262
Physician Recruitment
800 Park Boulevard, Suite 760
Boise, Idaho 83712

Primary Health

CALIFORNIA

Interim PHYSICIANS.

LOCUM TENENS
PERMANENT PLACEMENTS

Jim Ellis (800) 437-7676

PHYSICIANS WANTED

FAMILY PRACTICE

OREGON/SOUTHWEST WASHINGTON

Northwest Permanente, P.C., a stable, physician-managed multispecialty group of over 550 physicians providing quality care to 430,000 members of Kaiser Permanente in Oregon and Southwest Washington, has excellent opportunities for board certified or eligible family physicians. Our medical offices in Portland, Oregon have an outpatient clinical position that includes some urgent care; and our group in Longview has one position that requires OB skills

Our program offers a professionally stimulating practice in one of the most successful managed care systems in the country. We also offer a competitive salary (signing bonus for Longview), and a full benefits package including a generous retirement program, professional liability coverage, sabbatical leave and more. To receive additional information, please forward inquiry and CV to: W.J. Clark, Director of Professional Resources, Northwest Permanente, P.C., 500 NE Multnomah, Suite 100, Portland, OR 97232-2099. (800) 813-3763. EOE.

KAISER PERMANENTE
Northwest Permanente, P.C.
Physicians and Surgeons

PHYSICIANS WANTED

OREGON AND THE NORTHWEST. Urban, suburban, rural locations; variety of practice arrangements; all specialties. Placement professionals for 20 yrs. Oberto & Associates, 920 Pinecrest Terr, Ashland, OR 97520. (800) 482-6656; FAX (541) 482-4951. No J-1 Opp. boberto@jeffnet.org.

OCCUPATIONAL MEDICINE Locum Tenens Pacific Northwest - Northwest Permanente, P.C., a physician-managed, multispecialty group, has a full-time, six-month to one-year locum tenens opportunity available for a Board Certified and/or residency trained occupational medicine physician or other relevant primary care trained physician, at our medical offices in Oregon and Southwest Washington. Our Occupational Health Program has 19 physicians and covers outpatient clinics at nine sites with 65,000 visits per year, an Employee Health Service, and an Environmental Safety Program serving nearly 6,000 employees. We offer a competitive salary and benefit package which includes family medical insurance, paid time off, professional liability coverage, and a relocation allowance. Please forward C.V. to: W.J. Clark, Director of Professional Resources, NORTHWEST PERMANENTE, P.C., 500 NE Multnomah St., Suite 100, Portland, OR 97232-2099. (800) 813-3763. EOE.

INTERNIST - Contra Costa Regional Medical Center is seeking a well qualified, enthusiastic full-time BC/BE internist to join our staff to assist in teaching and supervising our Family Practice residents and to staff consult and continuity clinics. The position requires inpatient and outpatient skills in the entire spectrum of internal medicine, including the ICU, and might be particularly desirable to a recent Chief of Medicine Resident who laments the lack of job opportunities to teach and practice the full range of internal medicine. CCRMC offers a brand new facility, opened in January '98, extensive outpatient clinics, and a widely recognized family practice residency. We are located in the greater Bay Area, 20 miles from Berkeley, San Francisco and Oakland. Interested candidates may FAX or send a curriculum vitae to Shelley Pighin, Hospital Administration, 2500 Alhambra Avenue, Martinez, CA 94553. FAX (925) 370-5900 EOE.

HOSPITALIST/PULMONOLOGIST - NORTHERN CALIFORNIA - Excellent opportunity for BC/BE Hospitalist/Pulmonologist to join an 80+ physician multispecialty medical group in beautiful Santa Cruz, California, located on Monterey Bay, 90 miles south of San Francisco. If you are interested, please send current CV and three references with phone numbers to: President/CEO, Santa Cruz Medical Clinic, 2025 Soquel Avenue, Santa Cruz, CA 95062

MEDICAL NEWSLETTERS

HOW TO PASS BOARD OF INTERNAL MEDICINE

For first FREE issue (24 pages)
Send $5 to cover post & hand to:

ARORA BOARD REVIEW

389 East Mt. Pleasant Avenue
Livingston, NJ 07039

PHYSICIANS WANTED

FAMILY PRACTICE - SAN FRANCISCO BAY AREA - Contra Costa Health Services is looking forward to the opening of the Center for Health in North Richmond in January 1999. The Center will reflect the cultural and ethnic diversity of the community and provide a variety of medical and health education services to people of all ages. To staff this new facility, we are seeking two BC/BE Family Practitioners interested in being part of an interdisciplinary community. In addition to providing medical care, staff at the Center will be addressing such issues as TB, substance abuse, occupational/environmental health, domestic violence and HIV infection. If you are interested in this exciting opportunity, please send or fax your curriculum vitae to Shelley Pighin, Hospital Administration, 2500 Alhambra Avenue, Martinez, CA 94553. FAX (925) 370-5900 EOE.

FAMILY PRACTICE - SAN FRANCISCO BAY AREA - The Department of Family Medicine at the Contra Costa Regional Medical Center is seeking a competent, thorough and enthusiastic full-time or part-time BC/BE Family Practitioner to work as a clinician in our east county Family Practice Clinic. CCRMC is a teaching facility with a nationally recognized Family Practice Residency Program. This position offers challenging clinical work in the beautiful San Francisco Bay Area, full benefits and the potential for Resident training. Interested candidates please send or fax a curriculum vitae to Shelley Pighin, Administration, CCRMC, 2500 Alhambra Avenue, Martinez, CA 94553. FAX (925) 370-5900 EOE.

SALT LAKE CITY, UTAH–FACIAL, COSMETIC SURGERY - The Institute of Facial & Cosmetic Surgery is seeking a BC/BE plastic surgeon with outstanding technical skills and patient communication. Send CV and references to the Institute of Facial and Cosmetic Surgery at 5929 South Fashion Blvd. Murray, UT 84107 Fax: (801) 261-4096

INTERNAL MEDICINE - NORTHERN CALIFORNIA - Excellent opportunity for BC/BE General Internist to join an 80+ physician multispecialty medical group in beautiful Santa Cruz, California, located on Monterey Bay, 90 miles south of San Francisco. If you are interested, please send current CV and three references with phone numbers to: President/CEO, Santa Cruz Medical Clinic, 2025 Soquel Avenue, Santa Cruz, CA 95062

INTERNAL MEDICINE - Full time physician vacancies exist in the Pacific Northwest for Internal Medicine, (BC) with board eligibility in Endocrinology, Nephrology, Oncology, or Rheumatology. Family Practitioners, (BC or BE) may also find opportunities. Locum tenens candidates of all specialties, send information and preferences. Mail CV's to Elliot G. Boisen, MD, 2121 Westlake Ave. N., Suite 401, Seattle, WA, 98109 or call (206) 285-6955.

FAMILY PRACTICE - PHYSICIAN, F/T w/benefits - for rural FQHC/community Hlth Ctr. Provides prof. medical services, Interest in OB-GYN preferred. Supervises Mid-level providers. Degree from an accredited medical school, valid and current CA license, DEA license & Physician Assist. Supervisor license required. Bi-lingual, Eng/Span. pref. mail/fax CV 351 Felice Drive, Hollister, CA 95023; (408) 637-9640. Contact: Gigi @ 408-637-2237 EOE/AA. San Benito Health Foundation is a non-profit organization dedicated to providing affordable quality healthcare to all residents of San Benito County.

PHYSICIANS WANTED

PSYCHIATRIST: Full Time Adult Outpatient Psychiatrist no call. In an advanced multi-disciplinary team, community mental health setting. Please call Kathy Lopez. Human Resources, Randall Stenson, M.D. or Roger Speed, Director, (209)468-8750.

WESTERN STATES OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 100 positions of various specialties. Both permanent and locum tenens. Send CV to:

Western States Physician Services
7510 No. Trellis Circle, Fresno, CA 93720
Call (800) 873-0786; FAX (800) 705-7943
email: weserve@lightspeed.net

PHYSICIANS WANTED

Since 1979
the

LOCUM TENENS NETWORK has been taking the hassles of the paperwork and overhead out of practicing medicine. Practice near home or travel the country. We will coordinate all your travel details and provide you with the best occurrence malpractice policy available. Explore a partnership with Interim Physicians and open new horizons for your future.

Call today! (800) 333-7828

IOWA *AND* WISCONSIN

Join a 35 member Family Practice department, the largest department within one of the nations most prominent multi-specialty groups. Select from a practice in a picturesque college community surrounded by wooded hills and limestone bluffs. Or choose a practice in a historic community nestled amongst the deep, fertile valleys and towering bluffs of the Upper Mississippi Valley. Live in a lakeside community with a brand new clinic in which to practice. These family friendly communities offer you an excellent quality of life and abundant year round recreational opportunities. This group, with over one hundred years of service to the upper Midwest, can provide you the support needed to reach your professional and personal goals! *Contact Adam Jones* (800) 243-4353.

Strelcheck and Associates
1009 W. Glen Oaks Lane, #211
Mequon, WI 53092

ADVERTISING INDEX

Southern Medical Association . . .2nd Cover

MEDICINE + PSYCHIATRY . . . . . .3rd Cover

THE QUEST FOR MERCY . . . . . .4th Cover

ıe Western Journal of Medicine

ıctical Information for Practicing Physicians

Subscribe Now!

Western Journal of Medicine extends its thanks to the loyal CMA members ɔ have already made their commitment by subscribing to *WJM*. Here is your ɔortunity to support the revitalized *Journal*...**now available through subiption only**.

Your subscription to *WJM* features:

EPITOMES
Highlights of major advances in a different specialty each month with brief epitomes by experts in the field.

BIOMEDICAL SCIENCE
Five clinical research societies coordinate important new research findings, emphasizing clinical value.

SOCIOECONOMICS
WJM is often the first to predict, examine, and evaluate socioeconomic changes and trends.

CONFERENCES
All you need to know about medical conferences, nationally and locally.

ıe future of *WJM* is brighter than ever. Subscribe now so you won't miss a single monthly issue. Only **$45** per year for affiliated association members (**$65** for regular subscribers).

ıere are four easy ways to subscribe...

1 ***Call (804) 817-2000*** or **2** ***Fax this ad to (804) 817-2020*** or **3** ***Sign up online at www.wjmed.com*** or

4 ***Mail this ad to the address below***

...and there are three easy ways to pay:

ɜe my: ☐ Visa ☐ MasterCard ☐ Check enclosed ☐ Bill me

ɜ on card _____

_____ Exp. Date _____

ture _____

ɜ _____

ɜss _____

State, Zip _____

ɜ _____

_____ E-Mail _____

The Western Journal of Medicine

Check One (12 issues):

☐ $45 Member Rate

☐ $65 Regular Rate

☐ $20 Student/Resident/Intern

☐ $90 Institutional Rate

rn to: *The Western Journal of Medicine*, 1224 West Main Street, Suite 200, Charlottesville, VA 22903-2858.
ɜ (804) 817-2000. Fax (804) 817-2020.

Changing Your Address?

If you are moving and/or would like your Journal sent to a new address...

1. Print your old mailing address below or attach an old mailing label below:

Name _____

Old Address _____

City _____

State _____

Zip _____

Telephone _____

2. Print or type your new mailing address:

Name _____

New Address _____

City _____

State _____

Zip _____

Telephone _____

Fax _____

E-Mail _____

3. Clip and mail this form to:

The Western Journal of Medicine
1224 West Main Street, Suite 200
Charlottesville, VA 22903-2858

4. Or, visit our web-site at:

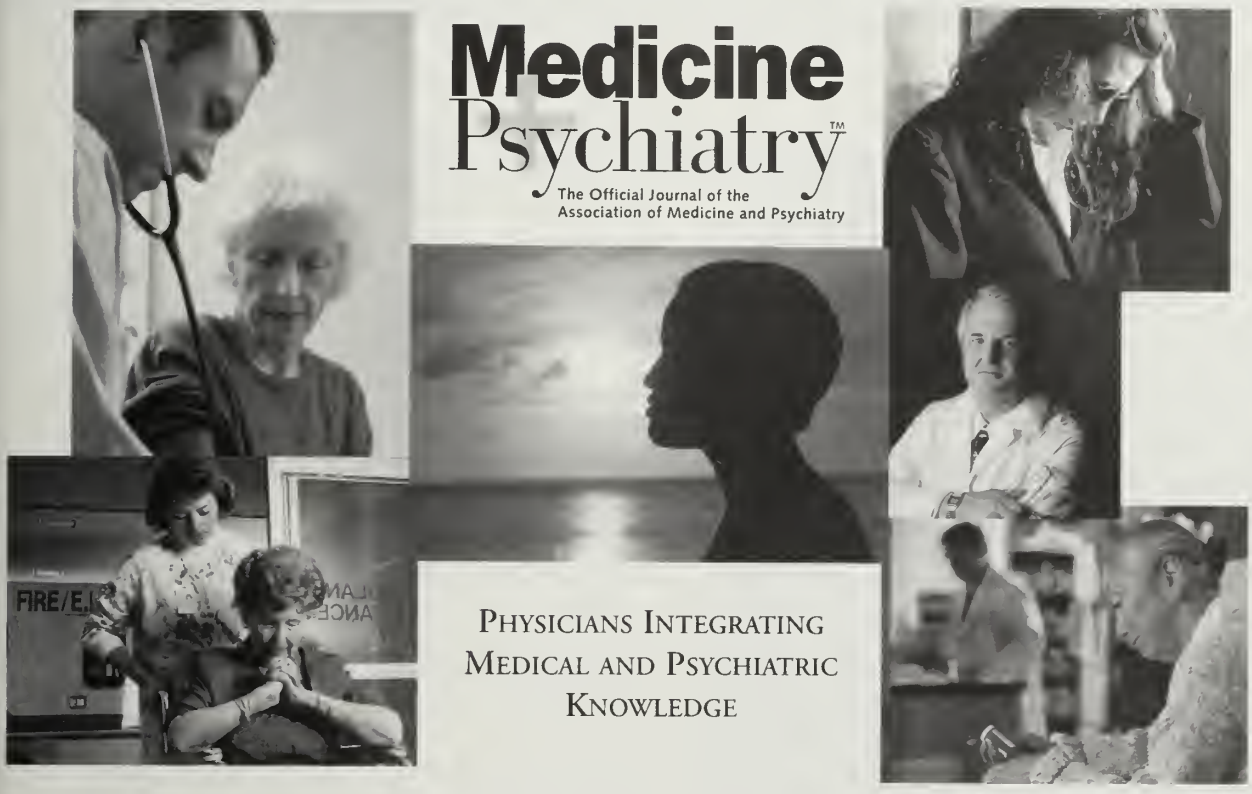
http://www.wjmed.com

The Western Journal of Medicine

www.wjmed.com

Practical Information for Practicing Physicians

Charter Subscription Rate!



- Original articles, reviews and case reports
- Clinical case conferences from Massachusetts General Hospital
- Content originating from the psychiatric problems that present in the primary care setting, emergency room, medical/psychiatric unit, geriatric unit, and consultation service

Charge my: ❑ Visa ❑ MasterCard ❑ Check enclosed ❑ Bill me

Card #_____

Exp. Date _____

Signature _____

Name _____

Institution/Title _____

Medical Specialty _____

Percentage of professional time spent: ___%Clinical ___%Research

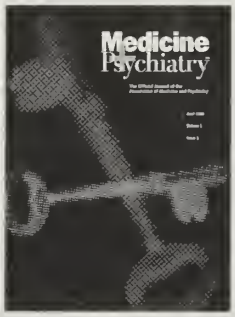
___%Teaching ___%Admin. ___%Other _____

Address _____

City, State, Zip _____

Phone _____

Fax _____



Check One (4 issues)

- ❑ $100 Individual Charter Rate
- ❑ $200 Institutional Rate
- ❑ $75 In-Training Rate
- ❑ $250 Outside North America

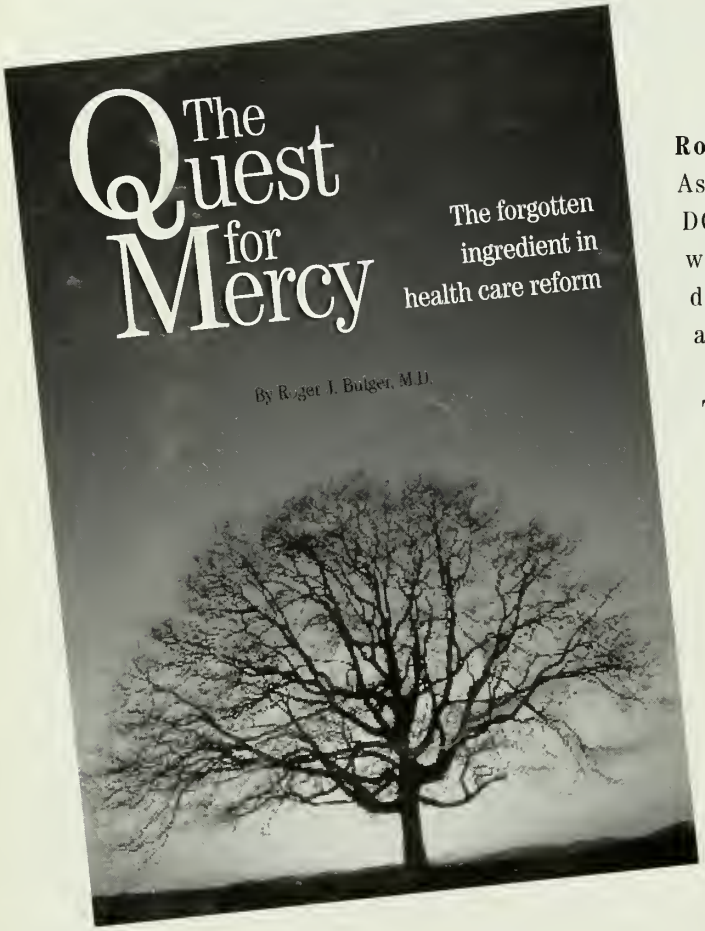
MP98

Return to: Medicine + Psychiatry, 1224 West Main Street, Suite 200
Charlottesville, VA 22903-2858 Phone (804) 979-4913 Fax (804) 979-4025

The Quest for Mercy

The forgotten ingredient in health care reform

by Roger J. Bulger, MD, FACP



Roger J. Bulger, MD, FACP is President of the Association of Academic Health Centers in Washington, DC. He has published scores of papers and chapters, as well as three books on subjects ranging from infectious diseases to medical education, humanities, Hippocrates, and, of course, academic health centers.

The Quest for Mercy is aimed at physicians, including young physicians and medical students. The book addresses managed care and managed cost, sickness and healing, hope and despair, relationships, oaths, populations, prevention, and patients.

"This book will become a classic."

Linda Hawes Clever, MD
Editor, THE WESTERN JOURNAL OF MEDICINE

The Complete Manuscript As Published I
The Western Journal of Medicin

ORDER YOUR COPIES NOW!

Per Copy: $10.00*

*Note: USA/Canada postage and handling included, all other countries please add US $6.00 Air Printed Matter postage. Please add Virginia and local sales tax where applicable. Quantity discounts available; please call.

I would like to order_____copy(ies) of **The Quest For Mercy**.

Payment must accompany order. Total amount enclosed $_____

NAME _____

INSTITUTION _____

ADDRESS _____

CITY/STATE/ZIP _____

COUNTRY _____

❑ Check Enclosed $_____ *please charge my* ❑ VISA ❑ MASTERCARD
(*make payable to:* The Western Journal of Medicine)

Account #_____ Exp. date _____

Signature _____

MAIL TO: *The Western Journal of Medicine*, 1224 West Main Street, Suite 200, Charlottesville, Virginia 22903-2858
Phone: (804) 979-8034 • Fax: (804) 979-4025 • www.wjmed.com

CARDEN JENNINGS
PUBLISHING CO., LTD.

OFFICIAL JOURNAL OF

ARIZONA MEDICAL ASSOCIATION · CALIFORNIA MEDICAL ASSOCIATION · DENVER MEDICAL SOCIETY · IDAHO MEDICAL ASSOCIATION · NEVADA STATE MEDICAL ASSOCIATION · NEW MEXICO MEDICAL SOCIETY · UTAH MEDICAL ASSOCIATION · WASHINGTON STATE MEDICAL ASSOCIATION · WYOMING MEDICAL SOCIETY

DISPLAY SHELVES

The Western Journal of Medicine

VOLUME 169 • NUMBER 3 SEPTEMBER 1998

ARTICLES

139 Ischemic Heart Disease and Stroke Mortality in African-American, Hispanic, and Non-Hispanic White Men and Women, 1985 to 1991
A J KARTER, J M GAZZANIGA, R D COHEN, M L CASPER, B D DAVIS, and G A KAPLAN

146 Failure of Physician Documentation of Sleep Complaints in Hospitalized Patients
H-H MEISSNER, A RIEMER, S SANTIAGO, M STEIN, M D GOLDMAN, and A J WILLIAMS

150 Effect of Mammography Outreach in Women Veterans
K M DALESSANDRI, M COOPER, and T RUCKER

153 Use of and Interest in Alternative Therapies Among Adult Primary Care Clinicians and Adult Members in a Large Health Maintenance Organization
N P GORDON, D S SOBEL, and E Z TARAZONA

162 Are Critically Ill Older Patients Treated Differently Than Similarly Ill Younger Patients?
A E STILLMAN, L E BRAITMAN, and R J GRANT

EPITOMES

166 Important Advances in Urology

ALERTS, NOTICES, AND CASE REPORTS

171 Unusual Vaginal Laceration Due to a High-Pressure Water Jet
J P RAMOS, D CARRISON, and D L PHILLIPS

173 Mastoiditis, Lymphoma, and AIDS
T LOWRY, L RAJA, and A VERGHESE

Medical Informatics

176 The Benefits and Challenges of an Electronic Medical Record: Much More than a "Word-Processed" Patient Chart
WV SUJANSKY

LESSONS FROM THE PRACTICE

184 The Unlikely Role Model
L L HILL

THOMAS A. COUNTWAY LIBRARY BOSTON, MA SEP 24 1998

OTHER FEATURES

132 Continuing Medical Education Activities
186 Instructions for Authors
189 Classified Advertising

Detailed Table of Contents: 130, 131

Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Medical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology

MEDICAL EXCELLENCE

SMA – Your CME Resource

Southern Medical Association 92nd Annual Scientific Assembly

November 18-22, 1998
New Orleans, Louisiana
Ernest N. Morial Convention Center

Guest Speakers

These speakers were confirmed at press time. More will be confirmed later.

Allergy & Immunology
Ernest N. Charlesworth, M.D., Brenham, Tex.
I. Celine Hanson, M.D., Houston, Tex.

Cardiology
Bruce Lindsay, M.D., St. Louis, Mo.

Colon & Rectal Surgery
John Pemberton, M.D., Rochester, Minn.
George Fuhrman, M.D., New Orleans, La.

Dermatology
Vincent A. DeLeo, M.D., New York, N.Y.
Stephen E. Wolverton, M.D., Indianapolis, Ind.

Emergency Medicine
Larry Mellick, M.D., Augusta, Ga.
Rick Dart, M.D., Denver, Colo.

Family Practice
Martin Sullivan, M.D., Durham, N.C.
Frank Svec, M.D., Ph.D., New Orleans, La.

Gastroenterology
Charles Sninsky, M.D., Gainesville, Fla.
Eugene R. Schiff, M.D., Miami, Fla.

Geriatric Medicine
Charles A. Cefalu, M.D., New Orleans, La.
Laura Chiodo, M.D., San Antonio, Tex.

Gynecology
G. Rodney Meeks, M.D., Jackson, Miss.

Medical Management & Administration
Robert L. Marier, M.D., New Orleans, La.
Jane M. Orient, M.D., Tucson, Ariz.

Medicine
Dick Briggs, Jr., M.D., Birmingham, Ala.
Blase Carabello, M.D., Charleston, S.C.

Neurology & Psychiatry
Christopher C. Colenda, M.D., East Lansing, Mich.
Salvador Ceniceros, M.D., Johnson City, Tenn.

Neurosurgery
Peter J. Jannetta, M.D., Pittsburgh, Penn.
John D. Jackson, M.D., New Orleans, La.

Occupational & Environmental Medicine
Edward J. Doyle, Jr., M.D., M.S.C., Morgantown, W. Va.
John Walden, M.D., Huntington, W. Va.

Oncology
Kent Wallner, M.D., Seattle, Wash.
Susan Miesfeldt, M.D., Charlottesville, Va.

Ophthalmology
Kurt A. Buzard, M.D., F.A.C.S., Las Vegas, Nev.

Orthopaedic & Trauma Surgery
Gerald Engh, M.D., Arlington, Va.

Otolaryngology - Head & Neck Surgery
C. Blake Simpson, M.D., San Antonio, Tex.
Thomas B. Aufdemorte, D.D.S., San Antonio, Tex.

Pathology
John W. Bishop, M.D., Omaha, Neb.
Charles B. Root, M.D., West Dundee, Ill.

Pediatrics & Adolescent Medicine
Russell W. Steele, M.D., New Orleans, La.
Franklin G. Boineau III, M.D., New Orleans, La.

Plastic & Reconstructive Surgery
James Grotting, M.D., F.A.C.S., Birmingham, Ala.
John J. Coleman III, M.D., Indianapolis, Ind.

Radiology
Christopher R. B. Merritt, M.D., New Orleans, La.
Eva Rubin, M.D. Birmingham, Ala.

Rheumatology
Fred Wolfe, M.D., Wichita, Kan.
Virginia Steen, M.D., Washington, D.C.

Surgery
Edward L. Bradley III, M.D., Buffalo, N.Y.
J. David Richardson, M.D., Louisville, Ky.

Urology
Jonathan P. Jarow, M.D., Baltimore, Md.

CME Opportunities

- Twenty-eight Specialty Section meetings and a number of joint meetings
- Scientific and Clinical Symposia - "early bird" symposia with free breakfast and mid-day symposia with free lunch
- Case-driven Grand Rounds - Controversial Diagnoses 1998: Prostate Cancer; Domestic Violence; Incontinence; Neck Pain; Occupational Medicine and the Primary Care Physician
- "Dessert with the Experts" with Specialty Section guest speakers
- Special 2-hour "New Drugs Update" Symposium - part of SMA's Section Officers' Recognition Luncheon
- Managed Care Track on important nonclinical issues - contracting, capitation, forming physician organizations, improving practice efficiency, reimbursement and compliance
- Women's Health Track to focus on issues in women's health
- The President's Symposium - "Physician Leadership for the Next Century"

Special Events

Enhance your CME experiences with special events.

Opening Ceremony
Thursday, November 19, 8:30 - 10:00 AM
The keynote address by SMA President J. Lorin Mason, M.D., marks the official start of the 92nd Annual Scientific Assembly. Entertainment and introduction of other SMA leaders will round out the program. This program is free to registered participants.

Section Social Functions, New Member Reception, and Alumni Reunions
Thursday, November 19, times vary

Prayer Breakfast
Friday, November 20, 7:00 - 8:00 AM
Initiated last year, this popular event offers an environment of fellowship and worship. This program is free to registered participants.

President's Reception
Friday, November 20, 7:30 PM
Let the good times roll at the annual President's Reception, featuring a masked ball (costume optional) at Mardi Gras World. Tickets are $35/Adult and $15/Child 12 or younger.

President's-Doctor's Day Awards Luncheon
Saturday, November 21, 12:30 - 2:30 PM
Nationally known columnist and entertaining food critic Calvin Trillin will be the featured speaker. Tickets are $30 each.

President's Night Dinner Dance
Saturday, November 21, 6:30 - 11:30 PM
Great food and the heritage of Southern music will highlight the President's Night Dinner Dance. And the Pink Flamingos are back to add their special brand o entertainment. Tickets are $85/Adult and $35/Chil 12 or younger.

For more information, call 800-423-4992

And more!!

- Insurance & Retirement Programs
- Exhibit Hall Activities
- Recreational Activities (Golf & Tennis Tournaments, Fun Run/Walk)
- Enrichment Programs
- Programs for Active Retired Members
- Over 30 hours of CME Credit offered for only $195.00 for SMA Members, $295 for Joining Members, and $445 for Nonmembers, and free for Medical Student, Residents and Fellows

The Southern Medical Association is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

92nd Annual Scientific Assembly
November 18-22 • New Orleans, Louisiana

THE FRANCIS A. COUNTWAY LIBRARY OF MEDICINE
CARDEN JENNINGS

The Western Journal of Medicine®

SINCE 1902

A PUBLICATION OF CARDEN JENNINGS PUBLISHING CO, LTD • 1224 WEST MAIN STREET, SUITE 200 • CHARLOTTESVILLE, VIRGINIA 22903-2858
TELEPHONE (804) 817-2000; FACSIMILE (804) 817-2020; E.MAIL wjm@cjp.com

LINDA HAWES CLEVER, MD, *Editor*
EDWARD D HARRIS JR, MD, *Associate Editor*
WILLIAM T CARDEN JR, *Publisher*

ALLISON SPEARMAN, *Managing Editor*
DAVID ERN, *Marketing Director*

editorial communications to DR CLEVER • business communications to MS SPEARMAN

Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Medical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

SPECIAL EDITORS

Special Editor for Arizona
Marshall B. Block, Phoenix, Ariz

Special Editor for Denver
David Shander, Denver, Colo

Special Editor for Idaho
E. R. W. Fox, Coeur d'Alene, Idaho

Special Editor for Nevada
Anton P. Sohn, Reno, Nev

Special Editor for New Mexico
I. Brian Taylor, Carlsbad, NM

Special Editor for Utah
C. Basil Williams, Salt Lake City, Utah

Special Editor for Washington
David Hopkins, Federal Way, Wash

Special Editor for Wyoming
Joseph P. Murphy, Casper, Wyo

ASSISTANT EDITORS

Clinical Investigation
H. Benfer Kaltreider

Health and Public Policy
Ralph Crawshaw

International Health
Anvar Velji

Lessons From the Practice
Stephen J. McPhee
Jonathan E. Rodnick

Medical Staff Conferences
Nathan M. Bass

Poetry
Margaret Kaufman

Primary Care Medicine
Stephen J. McPhee
Terrie Mendelson

Radiologic Cases
Jonathan M. Levy

EDITORIAL BOARD

Editor Emeritus
Malcolm S. M. Watts, San Francisco, Calif

Anesthesiology
Carol Lake, Sacramento, Calif

Biostatistics and Epidemiology
Virginia L. Ernster, San Francisco, Calif

Cardiac and Thoracic Surgery
Norman E. Shumway, Stanford, Calif

Dermatology
Clifton R. White Jr, Portland, Ore

Emergency Medicine
William A. Boehm, Alamogordo, NM

General and Family Practice
Norman Kahn, Kansas City, Mo
Thomas E. Norris, Seattle, Wash
Joe Schoeber, Casper, Wyo

Internal Medicine
Albert Deisseroth, Houston, Texas
Alan Fogleman, Los Angelas, Calif
Patricia Gabow, Denver, Colo
John H. Holbrook, Salt Lake City, Utah
Philip Hopewell, San Francisco, Calif
Irwin J. Schatz, Honolulu, Hawaii
Walter E. Stamm, Seattle, Wash
Reginald Strickland, Albuquerque, NM
Stephen I. Wasserman, San Diego, Calif

Neurology
Robert Collins, Los Angeles, Calif
John Greenlee, Salt Lake City, Utah
Leslie Wiener, Los Angeles, Calif
Earl Zimmerman, Portland, Ore

Neurosurgery
George A. Ojemann, Seattle, Wash
Robert F. Spetzler, Phoenix, Ariz

Nuclear Medicine
Jerold M. Lowenstein, San Francisco, Calif

Obstetrics and Gynecology
Daniel Mishell Jr, Los Angeles, Calif

Occupational Medicine
Linda Rosenstock, Washington, DC

Ophthalmology
Sandy Feldman, La Jolla, Calif

Orthopedics
Thomas DeCoster, Albuquerque, NM

Pathology
Ronald Weinstein, Tuczon, Ariz

Pediatrics
Allen W. Mathies Jr, Pasadena, Calif
Diane Wara, San Francisco, Calif

Pharmacology
Rubin Bressler, Tucson, Ariz

Physical Medicine and Rehabilitation
Julie G. Madorsky, Pomona, Calif

Preventive Medicine and Public Health
Joseph L. Lyon, Salt Lake City, Utah

Psychiatry
J. Christian Gillin, San Diego, Calif
Lewis Judd, La Jolla, Calif

Radiology
Gary Glazer, Stanford, Calif
Michael L. Manco-Johnson, Denver, Colo
Albert A. Moss, Seattle, Wash

Surgery
Haile T. Debas, San Francisco, Calif
Alex G. Little, Las Vegas, Nev

Urology
Linda Shortliffe, Stanford, Calif

Senior Members at Large
Thomas Elmendorf, Davis, Calif
Edgar Wayburn, San Francisco, Calif

ADVISORY BOARD, CLINICAL INVESTIGATION

Brian A. Cason, San Francisco, Calif
John Christenson, Salt Lake City, Utah
Kari Connolly, San Francisco, Calif
Bruce W. Goldberg, Portland, Ore
Philip Goodman, Reno, Nev
Roy Jones, Albuquerque, NM
Howard Lien, Tucson, Ariz
Barbara M. Lippe, Los Angeles, Calif
Michael W. McDermott, San Francisco, Calif
Jeanette Mladenovic, Denver, Colo
Kenneth M. Moser, San Diego, Calif
James C. Orcutt, Seattle, Wash
John Owings, Sacramento, Calif
Robert Robbins, Stanford, Calif
Henry Rosen, Seattle, Wash
Mary H. Samuels, Portland, Ore
George A. Sarosi, San Jose, Calif
Jeffrey Saver, Los Angeles, Calif
David Schriger, Los Angeles, Calif
Jack H. Simon, Denver, Colo
Peggy Sue Weintrub, San Francisco, Calif
Owen M. Wolkowitz, San Francisco, Calif

DISPLAY & CLASSIFIED ADVERTISING INFORMATION

CONTACT: MJ Mrvica Associates, Inc, 2 West Taunton Ave, Berlin, NJ 08009 • (609) 768-9360/FAX (609) 753-0064
Advertisements—The journal is published the second week of the month. Display advertising must be received no later than the first of the month preceding issue. Advertising rates will be sent on request. Acceptance of advertising is contingent upon approval by the Publisher.
The journal reserves the right to reject any advertisement.

SUBSCRIPTION INFORMATION

The subscription price per year is $65 in the United States and Canada (US funds); $80 in all other countries. Institutional rate $90. Single copies are $10. Special issues are $10. Address all subscription communications to:
THE WESTERN JOURNAL OF MEDICINE Circulation, 1224 W Main St, Suite 200, Charlottesville, VA 22903-2858 • Tel: (804) 817-2000

Allow six weeks for subscriptions to begin. Past issues must be bought individually. So long as reserve stocks are available, missing issue requests from subscribers are honored for up to six months after the issue date. Thereafter, the single copy rate of $10 is applicable for each issue available. Special issues are $10.

Change of Address—Requests for change of address should give both the old and new address. Allow six weeks for changeover.

SUBMITTING MANUSCRIPTS

Manuscripts for consideration should be sent to the managing editor, Allison Spearman, 1224 W Main St, Suite 200, Charlottesville, VA 22903-2858.

"Instructions for Authors"—A complete guide to manuscript submission and *WJM* style available from the publisher. Manuscripts may be prepared in accordance with the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals."

PUBLISHER

Copyright © 1998 by Carden Jennings Publishing Co, Ltd • Owned and Published by Carden Jennings Publishing Co, Ltd

All material subject to this copyright appearing in THE WESTERN JOURNAL OF MEDICINE may be photocopied for the noncommercial purpose of scientific or educational advancement. Volumes begin with January and July.

THE WESTERN JOURNAL OF MEDICINE (ISSN 0093-0415/USPS 084 480) is published monthly by Carden Jennings Publishing Co, Ltd, 1224 W Main St, Charlottesville, VA 22903-2858. Periodicals postage paid at Easton, Pennsylvania.

POSTMASTER: Send address changes to *The Western Journal of Medicine*, Circulation, 1224 W Main St, Suite 200, Charlottesville, VA 22903-2858.

The Western Journal of Medicine

VOLUME 169 • NUMBER 3 • SEPTEMBER 1998

CONTENTS

ARTICLES

139 **Ischemic Heart Disease and Stroke Mortality in African-American, Hispanic, and Non-Hispanic White Men and Women, 1985 to 1991**

ANDREW J. KARTER, PhD; JEANNIE M. GAZZANIGA, PhD; RICHARD D. COHEN, MA; MICHELE L. CASPER, PhD; BONNIE D. DAVIS, PhD; and GEORGE A. KAPLAN, PhD

From the Division of Research, Kaiser Permanente, Northern California Region, Oakland; the Cardiovascular Disease Outreach, Resources, and Epidemiology (CORE), University of California, San Francisco, Institute for Health and Aging, San Francisco, and the California Department of Health Services, Sacramento ; the Human Population Laboratory, Public Health Institute, Berkeley, Calif ; the Cardiovascular Health Studies Branch, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia; and the Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor.

146 **Failure of Physician Documentation of Sleep Complaints in Hospitalized Patients**

HORST-HELMUT MEISSNER, MD; ANN RIEMER; SILVERIO M. SANTIAGO, MD; MYRON STEIN, MD; MICHAEL D. GOLDMAN, MD, ScD; and ADRIAN J. WILLIAMS, MB

From the Medical and Research Services, West Los Angeles Department of Veterans Affairs (VA) Medical Center, and the Department of Medicine, UCLA School of Medicine, Los Angeles, California, and Lane Fox Respiratory Unit, St Thomas' Hospital, London, England.

150 **Effect of Mammography Outreach in Women Veterans**

KATHIE M. DALESSANDRI, MD; MELISSA COOPER, RN; and TUMAINI RUCKER

From the Veterans Affairs Palo Alto Health Care System (VAPAHCS), Palo Alto, California, and the Department of Surgery, Stanford University School of Medicine, Stanford, California.

153 **Use of and Interest in Alternative Therapies Among Adult Primary Care Clinicians and Adult Members in a Large Health Maintenance Organization**

NANCY P. GORDON, ScD; DAVID S. SOBEL, MD, MPH; and ELFI Z. TARAZONA, MPH

From the Division of Research and the Department of Regional Health Education, Kaiser Permanente Medical Care Program, Oakland, California.

162 **Are Critically Ill Older Patients Treated Differently Than Similarly Ill Younger Patients?**

ALFRED E. STILLMAN, MD; LEONARD E. BRAITMAN, PhD; and RICHARD J. GRANT, MD

From the Division of Geriatrics and the Office for Research and Technology Development, Albert Einstein Medical Center, and the Department of Medicine, Temple University Medical School, Philadelphia, Pennsylvania.

EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

Urology

Items of progress in urology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, as to both scientific fact and important clinical significance.

166 **Informing Patients About the PSA Test: A New Requirement**

PHILLIP WISE, MD, and KATHRYN DUKE, MPH, JD

167 **The Urethral Sling and Stress Urinary Incontinence**

H. ROGER HADLEY, MD, and ELMER B. PINEDA, MD

168 **Peyronie's Disease: A Difficult Sexual Dysfunction Problem**

LAURENCE A. LEVINE, MD

ALERTS, NOTICES, AND CASE REPORTS

171 **Unusual Vaginal Laceration Due to a High-Pressure Water Jet**

JOSEPH P. RAMOS, MD; DALE CARRISON, DO, FACEP; and DAVID L. PHILLIPS, MD

From the Department of Emergency Medicine, University Medical Center of Southern Nevada, Nevada.

173 **Mastoiditis, Lymphoma, and AIDS**

THOMAS LOWRY, LAIQ RAJA, MD; and ABRAHAM VERGHESE, MD

From the Division of Infectious Diseases (Dr Verghese), Department of Internal Medicine (Mr Lowry and Dr Raja), Texas Tech University Health Sciences Center, El Paso.

MEDICAL INFORMATICS

176 **The Benefits and Challenges of an Electronic Medical Record: Much More than a "Word-Processed" Patient Chart**

WALTER V. SUJANSKY, MD, PhD

From Oceania, Incorporated, Palo Alto, California.

LESSONS FROM THE PRACTICE

184 **The Unlikely Role Model**

LINDA L. HILL, MD, MPH

From UCSD-SDSU General Preventive Medicine Residency Program, San Diego State University, San Diego, California

OTHER FEATURES

132 **Continuing Medical Education Activities**

186 **Instructions for Authors**

189 **Classified Advertising**

★ Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

Continuing Medical Education

ARIZONA • CALIFORNIA, HAWAII, NEVADA • COLORADO • IDAHO • NEW MEXICO • UTAH • WASHINGTON • WYOMING

ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

CARDIOLOGY

February 7–11, 1999—**International Congress XII on Endovascular Interventions.** Contact: Erika Scott (602) 266-2200 or fax (602) 265-8885. www.endovascularcongress.org

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (520) 626-7832; (800) 328-5868.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Paulette Richardson, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-3387. For more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

November 6–8—**10th Annual Anesthesiology Update: 1998.** UC Davis at La Monterey Plaza Hotel. Fri-Sun. 13 hrs. $350. Contact: UC Davis Office of Continuing Medical Education, 2315 Stockton Blvd, Camellia Cottage, Rm. 1019, Sacramento, CA 95817 (916) 734-5390

ALLERGY/IMMUNOLOGY

September 10—**Immunization Update: 1998.** Center for Disease Control at various sites around state. Thurs. 2.5 hrs. Call California Distance Learning Health Networks for satellite sites and fees (619) 594-3348.

November—**Influenza Pandemic Preparedness.** Center for Disease Control at various sites around state. Thurs. 2.5 hrs. Call California Distance Learning Health Networks for satellite sites and fees (619) 594-3348.

CARDIOLOGY

September 14–18—**Cardiology Board Review.** UCSF at Cathedral Hill Hotel, San Francisco. $725. Contact: Postgraduate Programs, Box 0656, UCSF, San Francisco, CA 94143-0656.

October 8–10—**The 22nd Annual Seminar: Cardiology Update 1998.** American College of Cardiology at San Francisco. Thurs.–Sat. 12 hrs. $485–$560. Contact: ACC Extramural Programs (800) 253-4636.

October 31—**Update in Electrocardiography and Arrythmias.** UCSF at Radisson Miyako Hotel, San Francisco. Sat. 7.5 hrs. $195. Contact: UCSF (415) 476-5208.

January 7–10, 1999—**NewEra Cardiac Care:Innovation and Technology.** Marriott's Mountain Shadows Resort, Scottsdale Arizona. Sponsored by the Cardiothoracic Research &Education Forum. Contact:Aligned Management Associates, Inc. P.O. Box 23220, San Diego CA 92193 (760) 751-8841. Fax (760) 751-8842. www.amainc.com

January 29–31, 1999—**Clinical Nuclear Cardiology:Case Review With the Experts. Cardiology Update 1998.** American College of Cardiology at San Francisco. Thurs.–Sat. Contact: ACC Extramural Programs (800) 253-4636.

February 18–20, 1999—**19th Annual Pathophysiology & Techniques of Cardiopulmonary Bypass.** San Diego Marriott Hotel & Marina. Sponsored by the Cardiothoracic Research &Education Forum. Contact:Aligned Management Associates, Inc. P.O. Box 23220, San Diego CA 92193 (619) 541-1444 or fax (619) 541-1447 www.amainc.com

DERMATOLOGY

September 19–20—**The Skin A to Z.** UCSF at UCSF Campus. Sat–Sun. 10 hrs. $275. Contact:USCF (415) 476-5808.

January 14–17, 1999—**Practical Dermatology for the Primary Care Physician, San Diego, CA.** Sponsored by Continuing Medical Education Associates. To be held at the Hyatt Regency, La Jolla, San Diego, CA. Method: AV, L, SB, W. Thurs–Sun. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

March 4–7, 1999—**Practical Dermatology for the Primary Care Physician, Orlando, FL.** Sponsored by Continuing Medical Education Associates. To be held at the Buena Vista Palace at Walt Disney World Village, Orlando, FL. Method: AV, L, SB, W. Thus–Sun. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

May 23–26, 1999—**Practical Dermatology for the Primary Care Physician, Las Vegas, NV.** Sponsored by Continuing Medical Education Associates. To be held at the Caesars Palace, Las Vegas, NV. Method: AV, L, SB, W. Sun–Wed. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

EMERGENCY MEDICINE

October 3-7—**National Conference on Wilderness and Travel Medicine.** AmericanCollege of Emergency Physicians at Pare Fifty Five Hotel, San Francisco, CA. 25 hrs. Credit. Contact: (888) 263-6338.

October 8–10—**17th Annual Advances in Pulmonary and Critical Care.** UCSF at Palace Hotel, San Francisco. Thurs.–Sat. 17 hrs. $495. Contact: UCSF (415) 476-5208.

October 19–20—**Trauma Uncensored: 1998.** UC Davis at Hyatt Regency, Sacramento. Mon.–Tue. 17 hrs. $250. Contact: (916) 734-5390.

October 19–23—**Emergency Medicine Symposium I.** UCSD at La Jolla Marriott, San Diego. Mon.–Fri. 32 hrs. $495. Contact: OCME (619) 534-3940.

October 26–30—**27th Annual Topics in Emergency Medicine.** UCSF at Radisson Miyako Hotel, San Francisco. Mon.–Fri. 32 hrs. $675. Contact: UCSF (415) 476-5208.

November 9–13—**Emergency Symposium III.** UCSD at La Jolla Marriott, San Diego. Mon.–Fri. 32 hrs. Contact: OCME (619) 534-3940.

December 4–5—**Trauma Care – Then and Now.** UCSF at Hotel Nikko, San Francisco. Fri.-Sat.. 12 hrs. $395-$450. Contact: UCSF (415) 476-5808.

December 14-18— **Emergency Symposium II.** UCSD at La Jolla Marriott, San Diego. Mon.–Fri. 32 hrs. Contact: OCME (619) 534-3940.

May 13-16, 1999—**Outdoor Emergency Medicine, Scottsdale, AZ.** Sponsored by Continuing Medical Education Associates. To be held at the Marriott Camelback Inn, Scottsdale, AZ. Method: AV, L, SB, W. Thurs–Sun. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

May 13-16, 1999—**Outdoor Emergency Medicine, Scottsdale, AZ.** Sponsored by Continuing Medical Education Associates. To be held at the Marriott Camelback Inn, Scottsdale, AZ. Method: AV, L, SB, W. Thurs–Sun. 32 hrs credit:AMA, AOA, AAFP. $750. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

ENDOCRINOLOGY

March 11–13, 1999—**The Fourth International Conference on Continuous Renal Replacement Therapies.** Hotel del Coronado in San Diego, California. Contact:Shirley Kolkey, Complete Conference Management, 1660 Hotel Circle North, #220, San Diego, CA 92108. (619) 299-6673 or fax (619) 299-6675.

ETHICS

October 22–34—**Seventh Annual Symposium on the Design and Methods of Clinical Trials.** UCSF at San Francisco. Thurs–Fri Contact:UCSF Office of Continuing Medical Education. (415) 476-4251.

FAMILY PRACTICE/PRIMARY CARE

September 13-15—**Health Care Leadership Institiute Physicans Leadership Program.** Huntington Hotel, San Francisco, CA. Contact Laura Johnson-Morasch California Academy of Family Physicans (CAFP), 114 Sansome Street, Suite 1305, San Francisco, CA 94104-3824. (415) 394-9121 or fax (415 394-9119. email: HCLI@FamilyDocs.org

September 19—**Osteoporosis.** UC Davis at UC Davis Medical Center, Sacramento. Sat. 2.5 hrs. $50. Contact: UCD Office of Continuing Medical Education. (916) 734-2587.

October 7–10—**Update in Clinical Obstetrics and Gynecology.** UCSF at Hyatt Regency, La Jolla. Thurs.–Sun. Contact: UCSF, Jonathan Eros. (415) 476-7978.

October 14–16—**13th Annual Primary Care Medicine: Principles and Practice.** UCSF at Cathedral Hill Hotel, San Francisco. Wed.–Fri. 20 hrs. $550. Contact: Postgraduate Programs, Box 0656, UCSF, San Francisco, CA 94143-0656. (415) 476-5208.

October 22–26—**Masters of Medicine.** Sponsored by Continuing Medical Education Associates. Marriott Marquis, New York, NY. Thurs.–Mon. 30 hrs. Credit: AMA, AOA, AAFP. $795. Contact: Victoria Gonzales, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

December 3–4—**Controversies in Women's Health.** UCSF at Cathedral Hill Hotel, San Francisco. Thurs.–Fri. 13 hrs. Credit. $370. Contact: UCSF (415)476-5208.

January 14–17, 1999—**Practical Dermatology for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Regency, SF. Thurs.–Sun. 20 hrs. $575. Contact: Victoria Gonzales, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

January 14–17, 1999—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Regency, SF. Thurs.–Sun. 20 hrs. $575. Contact: Victoria Gonzales, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

February 12–14, 1999—**California Academy of Family Physicians (CAFP) 51 st Annual Scientific Assembly.** San Diego Concourse, San Diego, CA. 40 hrs. Contact: Clark Franklin, CAFP, 114 Sansome Street, Suite 1305, San Francisco, CA 94104-3824. (415) 394-9121 or fax (415) 394-9119.

May 14–18, 1999—**Primary Care Essentials, San Francisco, CA.** Sponsored by Continuing Medical Education Associates. To be held at the Grand Hyatt on Union Square, San Francisco, CA. Method: AV, L, SB, W. Thurs–Sun. 32 hrs credit:AMA, AOA, AAFP. $750. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

KEY TO ABBREVIATIONS

DREW:	Charles R. Drew Postgraduate Medical School, Office of Continuing Medical Education, (213) 563-4800.
LLU:	Loma Linda University, Continuing Medical Education Programs, (909) 824-4963.
STAN:	Stanford University, Postgraduate Education, (415) 723-5594.
UCD:	University of California, Davis, Office of Continuing Medical Education, (916) 734-5390.
UCI:	University of California, Irvine, Memorial/UCI Center for Health Education, (714) 824-5926.
UCLA:	University of California, Los Angeles, Continuing Education in Medicine and Health Sciences, (310) 794-2620.
UCSD:	University of California, San Diego, Office of Continuing Medical Education, (619) 534-3940.
UCSF:	University of California, San Francisco, Extended Programs in Medical Education, (415) 476-4251.
USC:	University of Southern California, Postgraduate Division, (800) USC-1119.

GERIATRICS

September 18—**Ethnicity and the Dementias.** UCLA at Queen Mary, Long Beach. Fri. 7 hrs. $95. Contact:Lucio Arruda, 10945 Le Conte Ave. Ste. 2339, Los Angeles, CA 90095-1687. (310) 312-0531.

November 8–11—**Geriatrics Update 1998.** Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego, CA. Sun.–Wed. 20 hrs. Credit: AMA, AOA, AAFP. $525. Contact: Victoria Gonzales, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

INFECTIOUS DISEASE

September 10—**Immunization Update 1998 Satellite Course.** California Distance Learning Health Network at various sites throughout California. Thurs. 2.5 hrs. Fee varies. Contact:CDLHN (619) 594-3348.

October 29–30—**Globally Emerging Viral Infections.** UCSF at Crowne Plaza Hotel-Union Square, SF. Thurs-Fri. 12 hrs. $415-$470. Contact: UCSF (415) 476-5808.

November 5–8—**Advances in Infectious Disease.** Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego, CA. Thurs.–Sun. 20 hrs. Credit: AMA, AOA, AAFP. $525. Contact: Victoria Gonzales, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200; http://www.cmea.com

November 19—**Preparing for the Coming Influenza Pandemic Satellite Course.** California Distance Learning Health Network at various sites throughout California. Thurs. 2.5 hrs. Fee varies. Contact:CDLHN (619) 594-3348.

December 2–6—**Internal Medicine- 1998 Fall Program.** Sponsored by Continuing Medical Education Associates. Boca Raton Resort and Club, Boca Raton, FL. Wed.–Tues. 30 hrs. Credit: AMA, AOA, AAP, AAFP. $750. Contact: Victoria Gonzales, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

December 3—**Surveillance of Vaccine-Preventable Diseases Satellite Course.** California Distance Learning Health Network at various sites throughout California. Thurs. 2.5 hrs. Fee varies. Contact:CDLHN (619) 594-3348.

December 9—**AIDS-Associated Malignancies: Biology and Clinical Management.** UCSF at Palace Hotel, San Francisco. Wed. Credit 4.5 hours. $135. Contact: UCSF (415) 476-5208.

December 10–12—**Clinical Care of the AIDS Pateient**. UCSF at Palace Hotel, San Francisco. Thurs-Sat. Credit 24 hours. $455. Contact: UCSF (415) 476-5208.

INTERNAL MEDICINE

October 2–3—**Consensus Symposium on Improving Migraine Management.** JW Marriott Hotel, Washington, DC. Contact: Ann Mitchell, (609) 423-7222 or fax (609) 423-3420.

October 9–13—**Internal Medicine - 1998 Fall Program.** Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego, CA. Fri.–Tues. 30 hrs. Credit: AMA, AOA, AAP, AAFP. $750. Contact: Victoria Gonzales, P.O. Box 270469, San Diego, CA 92198-2469. (800) 993-2632 or (619) 674-5200. http//www.cmea.com.

March 19–25, 1999—**Internal Medicine, San Diego CA.** Sponsored by Continuing Medical Education Associates. To be held at the Hotel Coronado, San Diego, CA. Method: AV, L, SB, W. Fri–Thurs. 45 hrs credit:AMA, AOA, AAFP. $895. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

NEPHROLOGY

October 2–8—**13th Comprehensive Nephrology Review Course.** UCLA at Beverly Hilton Hotel, Beverly Hills. Fri-Thurs. 44.5 hrs. $800. Contact: UCLA (310) 794-2620.

NEUROLOGY

October 10—**Brain Attack'98** UCLA at Beverly Hilton Hotel, Beverly Hills,CA. Fee $85. Contact Sheryl Crowley, Office of Continuing Medical Education, UCLA School of Medicine. (310) 794-3324.

OB/GYN

October 23–27—**OB/GYN Review.** Red Lion Hotel, Glendale. $675. Sat.–Tues. 38 hrs. Contact: USC School of Medicine, Postgraduate Division, 1975 Zonal Ave., KAM 307, Los Angeles, CA 90033-1039; Phone (213) 342-2555 or (800) USC-1119; Fax (213) 342-2152 or (888) 665-8650; email usccme@hsc.usc.edu.

February 11–14, 1999—**Office Gynecology and Women's Health for the Primary Care Physician, San Diego, CA.** Sponsored by Continuing Medical Education Associates. To be held at the Hyatt Islandia, San Diego, CA. Method: AV, L, SB, W. Thurs–Sun. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

February 25–28, 1999—**Office Gynecology and Women's Health for the Primary Care Physician, Orlando, FL.** Sponsored by Continuing Medical Education Associates. To be held at the Buena Vista Palace at Walt Disney World Village, Orlando, FL. Method: AV, L, SB, W. Thurs–Sun. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

OCCUPATIONAL & ENVIRONMENTAL

October 5–9—**Occupational and Environmental Medicine I.** UCSF at Radisson Miyako Hotel, San Francisco. Mon.–Fri. 40 hrs. $725. Contact: Postgraduate Programs, Box 0656, UCSF, San Francisco, CA 94143-0656. (415) 476-5208.

ONCOLOGY

September 24–26—**22nd Annual Physicians Cancer Symposium.** Scripps-Health at Sheraton San Diego Hotel & Marina. Thurs.–Sat. 16.5 hrs. $425–$450. Contact: Stevens Cancer Center, Scripps Memorial Hospital, 9888 Genesee Ave., La Jolla, CA 92037. Tuthanne Crawford (619) 626-6794.

OTOLOGY

November 5–7—**San Francisco Otology and Neurotology Update-1998.** UCSF at Ritz-Carlton Hotel San Francisco. Thurs-Sat. 19 hrs. $475. Contact:UCSF (415) 476-5808.

ORTHOPEDICS

January 14–17, 1999—**Office Orthopedics and Bone Radiology for the Primary Care Physician, San Diego, CA.** Sponsored by Continuing Medical Education Associates. To be held at the Hyatt Regency, La Jolla, San Diego, CA. Method: AV, L, SB, W. Thurs–Sun. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

February 25–28, 1999—**Office Orthopedics and Bone Radiology for the Primary Care Physician, New Orleans, LA.** Sponsored by Continuing Medical Education Associates. To be held at the Royal Sonesta Hotel, New Orleans, LA. Method: AV, L, SB, W. Thurs–Sun. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

February 25–28, 1999—**Office Orthopedics and Bone Radiology for the Primary Care Physician, Las Vegas, NV.** Sponsored by Continuing Medical Education Associates. To be held at the Caesars Palace, Las Vegas, NV. Method: AV, L, SB, W. Sun–Wed. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

PEDIATRICS

September 18–19—**California Society of Pediatric Cardiology.** UC Davis at Seascape Resort, Aptos. Fri.–Sat. Contact: UCD (916) 734-5390.

September 26—**Child's Brain Day-Practical Management of Childhood CNS Disorders.** UCSF at UCSF. Sat. 6.5hrs. $150. Contact:UCSF (415) 476-5808.

January 29–31,1999—**37TH Clinical Conference Pediatric Anesthesiology.** Disneyland Hotel, 1150 W. Cerritos Avenue, Anaheim, CA 92802. Sponsored by The Pediatric Anesthesiology Foudation. $250-$295. Contact David J Steward, M.B., Program Director, Pediatric Anesthesiology Conference Box #3, Childrens Hospital Los Angeles, P.O. Box 54700, Los Angeles, CA 90054. (213) 669-2262 or fax (213) 660-8983.

February 14–17, 1999—**Pediatrics Update 1999, San Diego, CA.** Sponsored by Continuing Medical Education Associates. To be held at the Hyatt Islandia, San Diego, CA. Method: AV, L, SB, W. Sun–Wed. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

February 28–March 3, 1999—**Pediatrics Update 1999, Orlando, FL.** Sponsored by Continuing Medical Education Associates. To be held at the Buena Vista Palace at Walt Disney World Village, Orlando, FL. Method: AV, L, SB, W. Sun–Wed. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

PSYCHIATRY

November 6–8—**44th Annual Group Therapy Symposium.** UCSF at UCSF. Fri–Sun. 20 hrs. $295-$340. Contact:UCSF (415) 476-5808.

RADIOLOGY

October 3–4—**Ultrasound Update: 1998.** UC Davis at Doubletree Hotel, Sacramento. Sat.–Sun. 10 hrs. $235. Contact: (916) 734-5390.

October 23–25—**18th Annual Comprehensive Review of Vascular and Interventional Radiology.** The Hotel Del Coronado, San Diego. Credit 19 hrs. AMA. $300-$500. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773 or fax (770)552-9859; email: webmaster@ryalsmeet.com. www.ryalsmeet.com

October 26–November 1—**23rd Annual San Diego Postgraduate Radiology Review Course.** The Hotel Del Coronado, San Diego. Credit 39 hrs. AMA. $700-$995. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773 or fax (770)552-9859; email: webmaster@ryalsmeet.com. www.ryalsmeet.com.

October 29–November 1—**2nd Annual Intensive Review of Neuro, Head, and Neck Radiology.** The Four Seasons Resort Hotel, Newport Beach, California. Credit 28 hrs. AMA. $450-$725. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773 or fax (770)552-9859; email: webmaster@ryalsmeet.com. www.ryalsmeet.com

October 30–November 1—**Breast Imaging and Interventions Update.** The Hotel Del Coronado, San Diego. Credit 15 hrs. AMA. $275-$450. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773 or fax (770)552-9859; email: webmaster@ryalsmeet.com. www.ryalsmeet.com

February 25–28, 1999—**Up to Date Radiology in the Desert.** Mira Monte Resort, Indian Wells, California. Credit 26 hrs. AMA. $495-$750. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

SURGERY

SSeptember 18—**4th Annual Surgical Review.** UC Davis at TAFT, Fairfield. Fri. Contact: (916) 734-7203.

GENERAL/MULTIDISCIPLINARY

October 22–23—**Seventh Symposium on Clinical Trials: Design, Methods, and Controversies.** UCSF Laurel Heights Campus, San Francisco. Contact: UCSF Office of Continuing Medical Education (415) 476-4251 or fax (415) 476-0318.

October 26–28—**Telemedicine IV.** UC Davis at Hilton Hotel, Anaheim. Mon.–Wed. Contact: (916) 734-5390.

May 16–19, 1999—**Alternative Medicine, Scottsdale, AZ.** Sponsored by Continuing Medical Education Associates. To be held at the Mariott Camelback Inn, Scottsdale, AZ. Method: AV, L, SB, W. Sun–Wed. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

LOSS PREVENTION

October 13—**Preventing "Failure to Diagnose" Malpractice Claims.** Medical Insurance Exchange of California, at Doubletree Hotel, Redding. Tues. Free or $40 to non members. Contact: David Carp (800) 227-4527.

October 20—A **Quality Improvement Program to Protect Your Medical Practice.** Medical Insurance Exchange of California, at Holiday Inn Select, Fairfield. Tues 2 hrs. Free or $40 to non members. Contact: David Carp (800) 227-4527.

November 3—**Medical Records Documentation for Patient Safety and Physician Defensibility.** Medical Insurance Exchange of California, at Santa Fe Bar and Grill, Berkeley. Tues. Free or $40 to non members. Contact: David Carp (800) 227-4527.

November 10—**Preventing "Failure to Diagnose" Malpractice Claims.** Medical Insurance Exchange of California, at San Francisco Medical Society. Wed. Free or $40 to non members. Contact: David Carp (800) 227-4527.

November 11—**Medical Records Documentation for Patient Safety and Physician Defensibility.** Medical Insurance Exchange of California, at Embassy Suites Hotel, Walnut Creek. Wed. Free or $40 for non members. Contact: MIE (800) 227-4527.

LEARNING SPANISH

September 18–21 (Los Angeles); October 2–5 (San Diego); October 23–26 (Los Angeles); December 4–7 (San Diego); January 22–25 (Los Angeles)—**Conversation in Spanish.** Maricopa Health System. 36 hrs. $695. Contact: Rios Associates (520) 881-3295; (619) 218-4875; Fax (520) 325-4258.

HOME STUDY/SELF ASSESSMENT

California Physicians' Legal Handbook Series. California Medical Association. Contact: CMA, PO Box 7690, San Francisco 94120-7690. (800) 882-1262.

Breast Cancer, Early Detection and Control. Texas Medical Association. CD ROM. $70. 2 hrs. Contact: Texas Medical Association, (800) 880-1300; http://www.texmed.org/health_science/hs_poep.html

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Second Wednesday of Each Month—**Cardiovascular Education Series.** St Anthony Hospital at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

February 4–6, 1999—**Neurology For The Non-Neurologist.** Hyatt Regency, Cancun Mexico. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

February 5–7, 1999—**Arrhythmias: Interptretation, Diagnosis & Management** MGM Grand, Las Vegas, NV Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

February 12–14, 1999—**Clinical Endocrinology For Primary Care Physicans.** Beaver Run Resort, Breckenridge, CO.Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

February 19–21, 1999—**Managing Respiratory Diseases.** Marriot's Casa Marina,Key West,FL. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

February 25–27, 1999—**Dermatology For The Non-Dermatologist.** Atlantis Paradise Resort, Bahamas. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

February 26–28, 1999—**Coronary Heart Disease Update.** Hilton Tapatio Cliffs, Scottsdale, AZ. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

March 12–14, 1999—**Dermatology For The Non-Dermatologist.**Riviera Hotel & Casino, Las Vegas, NV. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

March 25–27, 1999—**Neurology For The Non-Neurologist.** Grand Beach Resort, St. Thomas, USVI. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

March 25–27, 1999—**Clinical Endocrinology For Primary Care Physicans.** Marriott's Beach Resort, St. Grand Cayman. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

March 26–28, 1999—**Managing Respiratory Diseases.** Buena Vista Palace,Orlando,FL. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 8–10, 1999—**Coronary Heart Disease Update.** Hyatt Regency, Aruba Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 8–10, 1999—**Clinical Endocrinology For Primary Care Physicans.** The Westin Resort, St John, USVI. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 9–11, 1999—**Arrhythmias: Interptretation, Diagnosis &Management** Hilton Tapatio Cliffs, Scottsdale, AZ. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 9–11, 1999—**Neurology For The Non-Neurologist.** Marriott's Casa Marina, Key West, FL. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 23–25,1999—**Managing Respiratory Diseases.** Bally's, Las Vegas, NV. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 23–25,1999—**Dermatology For The Non-Dermatologist.** Parc Fifty-five, San Francisco, CA. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 30–May 2, 1999—**Dermatology For The Non-Dermatologist.** South Sea Plantation, Captiva Island, FL. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 30–May 2, **Clinical Endocrinology For Primary Care Physicans.** Hyatt Regency, New Orleans, LA. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

May 14–16, 1999—**Managing Respiratory Diseases.** Hilton Resort, Hilton Head, SC. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

May 14–16, 1999—**Neurology For The Non-Neurologist.** Bally's, Las Vegas, NV. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

IDAHO

The listing of continuing medical education programs in Idaho is compiled by the Ada County Medical Society. To list CME programs here, please send information at least two months in advance to: Ada County Medical Society, Inc. 305 W. Jefferson, PO Box 2668, Boise, Idaho 83701. (208) 336-2930.

Brochures, course information, and registration forms are available from the contact person or organization.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

October 12–15—**Neuroradiology for the Practicing Radiologists--The Robert Jahnke Memorial Course.** Hotel Loretto, Santa Fe, New Mexico. Approx. 20 hrs.AMA. $695. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

Every First and Third Tuesday—**Building and Implementing Clinical Practice Guidelines at the Point of Care.** Contact: Thomas A. Naegele, DO, (505) 275-7267.

October 11–16—**Update and Review of Internal Medecine 1998.** Marriot Hotel, Albuquerque, New Mexico. 53 hrs. Credit AMA and American Academy of Family Physicians. Contact: The University of New Mexico Office of Continuing Medical Education, Health Sciences & Services Bldg., Room 140Campus Box 713, Albuquerque, NM 87131-5126. (505) 272-3942 or fax (505) 272-8604. http://hsc.unm.edu/cme.

SATELLITE COURSES

Contact: Joe Treat or Jim Cato, Immunization Program, (505) 827-2366

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

September 11—**Ophthalmology--Clinical Faculty Day.** John Moran Eye Center, Salt Lake City. 7 hrs. Credit AMA. Contact: (801) 581-8664; fax (801) 581-3647; email: Rosalie.Lammle@hsc.utah.edu.

September 17–20—**Innovative Techniques in Plastic Surgery.** Wort Hotel, Jackson, Wyoming. 16 hrs. Credit AMA. Contact: (801) 581-8664; fax (801) 581-3647; email: Rosalie.Lammle@hsc.utah.edu.

September 29–October 3—**International Workshop on Magnetic Resonance Angiography**. Prospector Square Hotel and Conference Center, Park City. Not designated Category 1. Contact: (801) 581-8664; fax (801) 581-3647; email: Rosalie.Lammle@hsc.utah.edu.

October 2–3—**Western Intermountain Neurological Organization.** University Park Hotel, Salt Lake City. 12 hrs. Credit AMA. Contact: (801) 581-8664; fax (801) 581-3647; email: Rosalie.Lammle@hsc.utah.edu.

October 9–11—**Intensive Interactive Head and Neck Imaging Course.** University Park Hotel, Salt Lake City. 23 hrs. Credit AMA PRA.October 6-8, Preconference mini-fellowship (limited to course attendees), University of Utah School of Medicine, Department of Radiology. Contact: (801) 581-8664; fax (801) 581-3647; email: Rosalie.Lammle@hsc.utah.edu.

January 6–10, 1999—**MRI at Snowbird**. Cliff Lodge, Snowbird, Utah. Credit 20 hrs. AMA. $400-$650. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773 or fax (770)552-9859; email: webmaster@ryalsmeet.com. www.ryalsmeet.com

MEDICAL GRAND ROUNDS

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics.** Contact: UUSM.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Ave, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 S Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 340-2058.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Ste 1100, Seattle, WA 98121. (206) 441-9762.

OTHER CME OPPORTUNITIES

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE. November 6–8, 1998—**Scottsdale Headache Symposium.** Scottsdale at Marriott's Camelback Inn Resort & Spa. Contact: (609) 845-1720.

Annual Meeting and Course: International Spine Imaging Symposium. February 15–17, 1999. Registry Resort, Naples, Florida. Credit 19.5 hrs. AMA. $250-$650. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

The Atopy Syndrome in the Third Millenium. October 2–3, 1998, Zurich, Switzerland, on the occasion of the 50th anniversary of the allergy unit at the Dept of Dermatology, University Hospital, Zurich, and in collaboration with the European Academy of Allergology and Clinical Immunology. Contact: Prof. Dr. B. Wüthrich, Zurich, 41-1-255-3079, fax 41-1-255-4431.

Breast Imaging Today and Tomorrow. November 2–5, 1998. The Ritz-Carlton Resort Hotel, Naples Florida. Credit 26 hrs. AMA. $650. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

Breast Imaging Today and Tomorrow. January 25–28, 1999. Boca Raton Resort and Club, Boca Raton, Florida. Credit 23 hrs. AMA. $495-$695. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

Breast Imaging Today and Tomorrow. February 15–19, 1999. Buena Vista Palace Resort and Spa, Lake Buena Vista, Florida. Credit 23 hrs. AMA. $495-$695. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

CT-MRI State of the Art. October 15–18, 1998. The Hamilton Princess, Hamilton, Bermuda. 18 hrs. $320-$450. Contact: Ryals and Associates, Inc., P.O. Box 1925, Roswell, GA 30077-1925. (770) 641-9773 or fax (770) 552-9859.

Internal Derangements of Joints October 9–11, 1998. The Westin River North, Chicago, Illinois. Credit 19 hrs. AMA. $695. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

THE INTERNATIONAL SKELETAL SOCIETY- September 9–12, 1998—**25th Annual Refresher Course: Diagnosis & Management of Musculoskeletal Disorders**. Jury's Hotel, Dublin, Ireland. Credit 25 hrs. AMA. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

The Missed or Delayed Diagnosis of Breast Cancer. October 15–18, 1998. Four Seasons Hotel, Atlanta, Georgia. Credit 18 hrs. AMA. $450-$695. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

Mt. Sanai 1998 Body Imaging Update. October 10–13, 1998. The Plaza Hotel, New York, NY. Credit 22.5 hrs. AMA. $695. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

Musculoskeletal MR. October 22–25, 1998. The Westin Resort Hotel, Hilton Head, South Carolina. Credit 18 hrs. AMA. $650. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

Musculoskeletal MR. January 18–22, 1999. The Ritz-Carlton Resort Hotel, West Palm Beach, Florida. Credit 22.5 hrs. AMA. $450-$695. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

5th Annual Neuroradiology: A Comprehensive Review. February 2–6, 1999. The Ritz-Carlton Resort Hotel, West Palm Beach, Florida. Credit 24 hrs. AMA. $450-$695. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

58th Annual American Occupational Health Conference. April 23–30, 1999. Ernest N. Morial Convention Center, New Orleans, Louisiana. Contact: ACOEM Education Dept., 55 W. Seeger Road, Arlington Heights, IL 60005; (847) 228-6850 or fax (847) 228-1856; www.acoem.org.

NOTICE

State Associations should send their CME listings for publication to:

Allison Spearman, Managing Editor
Western Journal of Medicine
1224 W Main St, Ste 200
Charlottesville, VA 22903-2858

(804) 979-8034 • Fax (804) 979-4025 • wjm@cjp.com

HIV/AIDS Prevention, Early Intervention and Health Promotion:

A Self-Study Module for Rural Health Care Providers

On the Internet: **http://www.uchsc.edu/sm/aids**

(Providers unable to access the Internet may call toll-free: 1-888-861-8536 to request a printed edition.)

The self-study module prepares health care providers to:

- educate their patients to identify and reduce their risk for HIV infection
- identify HIV-infected patients as early as possible to maximize health outcomes
- encourage HIV-infected patients to employ strategies to maintain active, symptom-free lives.

Continuing Education Activity

- Free of charge
- CME and CEUs available for physicians, physician assistants, and nurses

Mountain-Plains Regional
AIDS Education and Training Center
University of Colorado Health Sciences Center

This project is funded by the Health Resources and Services Administration, Special Projects of National Significance Cooperative Agreement BRU 900108.

Articles

Ischemic Heart Disease and Stroke Mortality in African-American, Hispanic, and Non-Hispanic White Men and Women, 1985 to 1991

ANDREW J. KARTER, PhD, *Oakland, California*; JEANNIE M. GAZZANIGA, PhD, *Sacramento, California*; RICHARD D. COHEN, MA, *Berkeley, California*; MICHELE L. CASPER, PhD, *Atlanta, Georgia*; BONNIE D. DAVIS, PhD, *Sacramento, California*; *and* GEORGE A. KAPLAN, PhD, *Ann Arbor, Michigan*

We compare recent trends in ischemic heart disease (IHD) and stroke mortality in California among the 6 major sex-racial or -ethnic groups. Rates of age-specific and -adjusted mortality were calculated for persons aged 35 and older during the years 1985 to 1991. Log-linear regression modeling was performed to estimate the average annual percentage change in mortality. During 1985 through 1991, the mortality for IHD and stroke was generally highest for African Americans, intermediate for non-Hispanic whites, and lowest for Hispanics. Age-adjusted mortality for IHD declined significantly in all sex-racial or -ethnic groups except African-American women, and stroke rates declined significantly in all groups except African-American and Hispanic men. African Americans had excess IHD mortality relative to non-Hispanic whites until late in life, after which mortality of non-Hispanic whites was higher. Similarly, African Americans and Hispanics had excess stroke mortality relative to non-Hispanic whites early in life, whereas stroke mortality in non-Hispanic whites was higher at older ages. The lower IHD and stroke mortality among Hispanics was paradoxical, given the generally adverse risk profile and socioeconomic status observed among Hispanics. An alarmingly high prevalence of self-reported cardiovascular disease risk factors in 1994 to 1996, particularly hypertension, leisure-time sedentary lifestyle, and obesity, is a serious public health concern, with implications for future trends in cardiovascular disease mortality. Of particular concern was the growing disparities in stroke and IHD mortality among younger-aged African Americans relative to Hispanics and non-Hispanic whites.

(Karter AJ, Gazzaniga JM, Cohen RD, Casper ML, Davis BD, Kaplan GA. Ischemic heart disease and stroke mortality in African-American, Hispanic, and non-Hispanic white men and women, 1985 to 1991. West J Med 1998; 169:139–145)

In the United States, mortality attributable to the two major forms of cardiovascular disease (CVD), ischemic heart disease (IHD) and stroke, has varied considerably among the three major racial or ethnic groups, African Americans, non-Hispanic whites, and Hispanics.[1] Overall, CVD mortality has dropped considerably since 1970, although the rate of the decline appears to be slowing.[2,3] Trends in minority populations have not been as favorable, resulting in a widening racial or ethnic disparity.[4–6] Consequently, the identification and continued monitoring of high-risk subgroups are important components of CVD-prevention efforts.

Although trends in CVD mortality in African Americans and non-Hispanic whites have been well documented, recent published information for this country's fasting growing minority, Hispanics, is relatively scarce, especially with regard to stroke.[7,8] Documenting trends in Hispanics is of particular interest because of their paradoxically low CVD mortality despite unfavorable cardiovascular risk profiles.[9,10] Historically, less than half of the states have collected Hispanic race or ethnicity on death records, and in most cases, the practice began within the past decade. The distribution of CVD risk factors varies among the three major Hispanic subgroups—Mexican Americans, Cuban Americans, and Puerto Ricans[11]—and, in turn, the distributions of these subgroups vary widely from state to state, making the pooling of data problematic. California has reliably

From the Division of Research, Kaiser Permanente, Northern California Region, Oakland (Dr Karter); the Cardiovascular Disease Outreach, Resources, and Epidemiology (CORE) Program, University of California, San Francisco, Institute for Health and Aging, San Francisco(Dr Gazzaniga), and the California Department of Health Services, Sacramento (Drs Gazzaniga and Davis); the Human Population Laboratory, Public Health Institute, Berkeley, Calif (Mr Cohen); the Cardiovascular Health Studies Branch, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Ga (Dr Casper); and the Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor (Dr Kaplan).

Reprint requests to Andrew J. Karter, PhD, Division of Research, Kaiser Permanente, 3505 Broadway, Oakland, CA 94611-5714 (e-mail: ajk@dor.kaiser.org).

ABBREVIATIONS USED IN TEXT

BRFSS = Behavioral Risk Factor Surveillance System
CVD = cardiovascular disease
ICD-9 = *International Classification of Diseases, 9th Revision*
IHD = ischemic heart disease
MI = myocardial infarction

recorded Hispanic origin on death certificates since 1985. The Hispanic population in California is overwhelmingly Mexican American and represents about 35% of Hispanics in the US population. In addition, California has a large African-American population, providing adequate statistical power for racial-ethnic comparisons. In this article, we examine the trends in IHD and stroke mortality among these three major racial-ethnic groups in California during the years 1985 to 1991 and recent results from the California Behavioral Risk Factor Surveillance System (BRFSS).

Methods

Mortality data for California residents were obtained from the death certificate computer files of the California Department of Health Services, Health Data and Statistics Branch, Health Demographics Section for 1985 to 1991. The computer files were searched for underlying-cause-of-death codes 410 to 414 (IHD) and 430 to 438 (stroke) according to the *International Classification of Diseases, 9th Revision* (ICD-9).[12] Race- or ethnicity-specific population estimates for California residents were obtained from the California Department of Finance.

Race- or ethnicity-specific, age-adjusted mortality rates for ages 35 and older were calculated using the 1980 US census as the standard for direct adjustment.[13] Numerators of the age-specific rates were based on IHD and stroke deaths in ten-year age intervals to increase the stability of each age-sex-racial or -ethnic stratum. The relative change (average annual percentage change in the rate) in IHD mortality was estimated using a log-linear model that assumes a constant proportional change.[14] Statistical interactions between the relative change and race or ethnicity were assessed as a test of statistical differences in the trends. Age-specific rate ratios were calculated using non–Hispanic-white age-specific rates as the referent group. Results from the California BRFSS for the years 1994 to 1996 were used to estimate the prevalence of selected cardiovascular risk factors, after age-adjusting to the 1990 California population. The BRFSS sample sizes for men and women, respectively, were as follows: African American, 274 and 406; Hispanic, 1,217 and 1,559; and non-Hispanic white, 3,413 and 4,296. In this article, the term "race or ethnicity" is meant to reflect the combination of defining human physical-biologic variations and adaptations, as well as the social context, including historical conditions, economic and social factors, and political and cultural forces.[15]

Results

Ischemic Heart Disease

For men, between 1985 and 1991, the age-adjusted rates of IHD mortality in California were consistently lowest for Hispanics, whereas those in African-American and non–Hispanic-white men were similar. For women, the age-adjusted rates of IHD mortality were consistently lowest for Hispanics and highest for African Americans. The racial or ethnic differences were substantial, with about a twofold higher age-adjusted IHD mortality in African-American and non–Hispanic-white men than in Hispanic men and in African-American women than in Hispanic women.

During this period, the age-adjusted IHD mortality declined more for men than for women in each of the three racial or ethnic groups (Table 1). For men, non-Hispanic whites had the largest, Hispanics intermediate, and African Americans the smallest decline in rates. For women, Hispanics again had the largest and non-Hispanic whites had slightly lesser declines, whereas African Americans showed no significant decline (95% confidence interval includes zero). Among African-American women, there was a slight increase in IHD mortality during the early years; however, by 1991 the rate had dropped back to the level observed in 1985. Racial-ethnic differences in these trends were not statistically significant for men ($P = .15$), but approached significance in women ($P = .08$).

During 1985 to 1991, the age-specific rates (Table 2) were consistently lowest for Hispanics among both men and women. Among men, the age-specific IHD mortality was lower for non-Hispanic whites than for African Americans until midlife, after which a "crossover" occurred, and African Americans had lower rates during the older ages. The age of mortality crossover for African-American and non-Hispanic whites changed over time as well, ranging from the 60s during 1985 to the 80s in 1991. A similar pattern was observed between non–Hispanic-white and African-American women, although the age at mortality crossover was later. In general, the age-specific IHD rates for those younger than 65 years have dropped between 1985 and 1991 (Table 2). The age-specific rate ratios suggest, however, that, except for men aged 35 to 44 years, the gap between the rates for African-American and non–Hispanic-white men and women has widened whereas that between Hispanic and non–Hispanic-white men and women has narrowed.

Stroke

For both men and women, the mortality for stroke was consistently highest for African Americans, lowest for Hispanics, and intermediate for non-Hispanic whites (Table 1). Substantial racial-ethnic variation occurred, with about a twofold higher age-adjusted rate in African Americans relative to Hispanic men and women during the entire period.

During 1985 through 1991, the age-adjusted stroke mortality declined slightly more for women than for men

TABLE 1.—*Average Annual Percentage Change* in Age-adjusted Mortality† of Ischemic Heart Disease and Stroke by Race or Ethnicity and Sex, Ages ≥35 Years, California, 1985 to 1991*

	Men			Women		
	Mortality Rate, /100,000		Avg Annual % Change	Mortality Rate, /100,000		Avg Annual % Change
	1985	1991	(95% CI)	1985	1991	(95% CI)
Ischemic heart disease						
African American	618	560	−2.1 (−2.9 to −1.3)	416	405	−0.3 (−1.8 to +1.3)
Hispanic	352	290	−2.8 (−4.1 to −1.5)	232	192	−2.4 (−4.1 to −0.8)
Non-Hispanic white	648	517	−3.5 (−3.8 to −3.1)	351	301	−2.3 (−3.2 to −1.5)
Stroke						
African American	178	197	+1.4 (−0.7 to +3.5)	193	176	−1.2 (−2.6 to +0.2)
Hispanic	99	96	−1.8 (−4.0 to +0.6)	89	76	−2.4 (−4.1 to −0.7)
Non-Hispanic white	140	124	−1.5 (−2.3 to −0.7)	135	115	−2.2 (−3.2 to −1.2)

Avg = average, CI = confidence interval

*Calculated using a log-linear regression model.
†Age-adjusted rate per 100,000 person-years, adjusted to the 1980 US population.

in each of the three racial-ethnic groups (Table 1). The rates showed no significant changes in African-American and Hispanic men or African-American women, but declines occurred in the remaining sex-racial or -ethnic groups. Racial or ethnic differences in these trends were not significant in women ($P = .58$), but approached significance in men ($P = .06$).

During 1985 to 1991, non-Hispanic whites had the lowest stroke mortality in the youngest age groups; however, their rates crossed over the Hispanic rates in the 65- to 74-year-old group and the African-American rates in the oldest age group (≥85 years). The 1985 to 1991 trends in age-specific stroke rates for those younger than 65 years have been mixed and have not shown as much improvement as in IHD (Table 2). As was the case with IHD, the age-specific rate ratios suggest that the gap between stroke rates for African-American and non–Hispanic-white men and women has widened. The gap between Hispanic and non–Hispanic-white men and women was also widening, however, while Hispanic age-specific strokes rates have exceeded those of non-Hispanic whites at the younger ages.

Cardiovascular Risk Factors

Table 3 details the age-adjusted prevalence estimates by race or ethnicity and sex for five major, self-reported, CVD behavioral risk factors: cigarette smoking, obesity, hypertension, diabetes mellitus, and leisure-time sedentary lifestyle. In general, the prevalence of current smoking was similar among sex-racial or -ethnic groups, except for Hispanic women, who reported a statistically lower prevalence. African-American men and women had the highest prevalence of hypertension. For African-American men, it was statistically higher than among Hispanic or non–Hispanic-white men, and for African-American women, it was statistically higher than among non–Hispanic-white women. The prevalences of obesity, diabetes mellitus, and leisure-time sedentary lifestyle were statistically lower among non-Hispanic whites than among the two minority populations. At nearly 70%, the prevalence of a sedentary lifestyle was statistically higher among Hispanic men than among African-American men or women.

Discussion

During 1985 to 1991, the age-adjusted mortality for IHD declined statistically in all sex-racial or -ethnic groups except African-American women. Stroke rates declined statistically in non–Hispanic-white men and women and Hispanic women whereas African-American men had an increase in rates, albeit nonsignificant. For each racial-ethnic group and across the time period, men had higher age-adjusted IHD mortality than women, but stroke mortality was similar among men and women. The racial-ethnic patterns for both CVDs were consistent with the general patterns observed at the national level; Hispanics had the lowest age-adjusted rates, non-Hispanic whites had intermediate rates, and African-Americans had the highest rates.[1] The relatively greater effects of CVD for African-American men and women were clearly evident; on average, African Americans were dying at the fastest rate and at the youngest age relative to Hispanics and non-Hispanic whites and had the least favorable trends between 1985 and 1991.

Although observing patterns in an age-adjusted rate over time is the simplest way to evaluate trends in CVD mortality, such a population-weighted average masks the important age-specific racial-ethnic differences in the groups that we observed. In addition, identifying excess mortality, in particular race- or ethnicity-age strata, will facilitate appropriate tailoring of CVD-prevention efforts. Non–Hispanic-white IHD rates increased more rapidly with age than those for African Americans or Hispanics. Subsequently, African-American men and women had an excess IHD mortality relative to non-His-

TABLE 2.—*Age-Specific Mortality (/100,000) and Rate Ratios* for Ischemic Heart Disease and Stroke Mortality by Race or Ethnicity*

	Ages, yr					
Disease Mortality	*35 to 44*	*45 to 54*	*55 to 64*	*65 to 74*	*75 to 84*	*≥85*
Ischemic heart disease †						
Men 1985						
African American	57 (1.73)	191 (1.20)	510 (1.14)	999 (0.93)	2,327 (0.88)	3,836 (0.82)
Hispanic	17 (0.51)	63 (0.39)	203 (0.46)	542 (0.50)	1,563 (0.59)	3,014 (0.64)
Non-Hispanic white	33 (1.00)	160 (1.00)	445 (1.00)	1,075 (1.00)	2,651 (1.00)	4,686 (1.00)
Men 1991						
African American	36 (1.62)	133 (1.40)	385 (1.28)	888 (1.14)	2,135 (1.05)	4,811 (0.89)
Hispanic	9 (0.42)	50 (0.53)	167 (0.56)	500 (0.64)	1059 (0.52)	2,952 (0.54)
Non-Hispanic white	22 (1.00)	95 (1.00)	302 (1.00)	780 (1.00)	2,033 (1.00)	5,423 (1.00)
Women 1985						
African American	19 (2.37)	69 (2.04)	256 (1.90)	726 (1.55)	1,678 (1.06)	3,459 (0.77)
Hispanic	2 (0.23)	16 (0.46)	100 (0.74)	336 (0.72)	966 (0.61)	3,048 (0.68)
Non-Hispanic white	8 (1.00)	34 (1.00)	135 (1.00)	468 (1.00)	1,581 (1.00)	4,474 (1.00)
Women 1991						
African American	17 (3.23)	57 (2.29)	202 (1.89)	596 (1.72)	1,612 (1.29)	4,785 (1.01)
Hispanic	2 (0.45)	21 (0.85)	83 (0.78)	264 (0.76)	790 (0.64)	2,531 (0.54)
Non-Hispanic white	5 (1.00)	25 (1.00)	107 (1.00)	346 (1.00)	1,246 (1.00)	4,731 (1.00)
Stroke †						
Men 1985						
African American	12 (2.02)	53 (3.36)	115 (2.08)	275 (1.49)	808 (1.15)	1,077 (0.72)
Hispanic	8 (1.36)	19 (1.19)	48 (0.87)	150 (0.81)	414 (0.59)	996 (0.67)
Non-Hispanic white	6 (1.00)	16 (1.00)	55 (1.00)	185 (1.00)	701 (1.00)	1,488 (1.00)
Men 1991						
African American	23 (3.88)	58 (4.25)	120 (2.70)	326 (2.17)	749 (1.37)	1,515 (0.88)
Hispanic	7 (1.21)	23 (1.72)	54 (1.22)	143 (0.95)	385 (0.70)	940 (0.55)
Non-Hispanic white	6 (1.00)	14 (1.00)	44 (1.00)	151 (1.00)	547 (1.00)	1,722 (1.00)
Women 1985						
African American	20 (3.56)	40 (2.64)	124 (3.03)	261 (1.74)	839 (1.35)	1,685 (0.87)
Hispanic	6 (1.12)	11 (0.73)	38 (0.94)	114 (0.76)	347 (0.56)	1,229 (0.63)
Non-Hispanic white	6 (1.00)	15 (1.00)	41 (1.00)	150 (1.00)	622 (1.00)	1,944 (1.00)
Women 1991						
African American	19 (4.11)	49 (3.88)	107 (3.09)	216 (1.84)	701 (1.42)	1,830 (0.98)
Hispanic	6 (1.37)	17 (1.33)	39 (1.12)	97 (0.83)	300 (0.61)	921 (0.49)
Non-Hispanic white	5 (1.00)	13 (1.00)	35 (1.00)	117 (1.00)	493 (1.00)	1,871 (1.00)

*Due to rounding of the age-specific rates, rate ratios may be slightly different from the race-ethnic age-specific rates divided by non-Hispanic white age-specific rates.
†Rate ratio relative to non-Hispanic whites.

panic whites until late in life, after which non–Hispanic-white mortality was higher. During 1985 to 1991, despite a slight drop in the age-specific rates, growing racial-ethnicity disparities in IHD were observed among the youngest ages. In particular, the youngest African-American women had high rate ratios of 3.23 in 1991 compared with 2.37 in 1985. Hispanics consistently had the lowest age-specific IHD rates, with age-specific rate ratios (relative to non-Hispanic whites) often below 0.75, although the gap narrowed during the observation period.

Stroke rates also increased most rapidly with age for non-Hispanic whites. Consequently, African-American and Hispanic men and women had an excess stroke mortality relative to non-Hispanic whites early in life, whereas non–Hispanic-white mortality was higher after a varying mortality crossover point in the age groups 55 to 64 years and 65 to 74 years. This mortality crossover has also been noted in other vital-statistics studies of stroke in Hispanics and non-Hispanic whites.[7,8] Despite a slight drop in the age-specific rates during 1985 to 1991, the excess stroke mortality relative to non-Hispanic whites increased; for example, in 1991, African-American men and women in the youngest age group had about a fourfold higher stroke mortality than did non-Hispanic whites. In addition, young Hispanics had, in general, higher age-specific stroke rates than non-Hispanic whites in 1991.

The substantially lower mortality of IHD in Hispanics relative to non-Hispanic whites among women, in addition to men, make our findings different from those

TABLE 3.—*Cardiovascular Disease Risk Factor Profiles Among California Residents Aged ≥18 Years, by Sex and Race or Ethnicity, 1994 to 1996*

	Men, 1994 to 1996		Women, 1994 to 1996	
Risk Factor	*Prevalence*	*95% CI*	*Prevalence*	*95% CI*
Current smoking, %				
African American	21.1	(15.8–26.4)	19.8	(15.5–24.2)
Hispanic	17.7	(15.3–20.2)	9.8	(8.1–11.4)
Non-Hispanic white	20.4	(18.8–22.0)	17.8	(16.4–19.1)
Hypertension, %				
African American	32.2	(25.9–38.5)	29.8	(24.8–34.9)
Hispanic	19.2	(16.2–22.3)	22.8	(20.1–25.5)
Non-Hispanic white	20.3	(18.8–21.7)	19.6	(18.3–20.9)
Obesity, %				
African American	35.4	(29.0–41.7)	40.6	(35.1–46.1)
Hispanic	38.7	(35.3–42.2)	35.4	(32.4–38.4)
Non-Hispanic white	25.0	(23.4–26.6)	22.1	(20.6–23.5)
Diabetes, %				
African American	9.0	(4.7–13.3)	9.1	(6.0–12.3)
Hispanic	8.4	(6.0–10.9)	7.6	(5.9–9.3)
Non-Hispanic white	3.5	(2.8–4.1)	3.1	(2.6–3.6)
Leisure time sedentary lifestyle, %				
African American	58.9	(52.4–65.5)	59.5	(54.1–64.9)
Hispanic	69.5	(66.4–72.6)	67.4	(64.7–70.1)
Non-Hispanic white	48.8	(46.9–50.8)	48.9	(47.2–50.7)

CI = confidence interval

of recent reports[16–20] (although not others[21]). Inconsistencies may be due to the inclusion of differing ICD-9 codes or temporal or geographic variations between studies. Hispanics also had the most favorable secular trends, with the steepest declines in rates of IHD in women and of stroke in men and women.

The Hispanic results are paradoxical considering the relatively low socioeconomic status of this racial-ethnic group and the well-established association between socioeconomic status and CVD mortality.[22–24] Hispanics have advantageous rates of other key health indicators, such as infant mortality, life expectancy, and measures of functional health, while having a greater proportion of persons living in poverty, without health insurance, and with reduced access to health care than non-Hispanic whites.[9,25,26] With 22% of Hispanics falling below the federally established poverty threshold, Hispanics have higher rates of poverty than African Americans (21%) or non-Hispanic whites (9%) in California.[27] A national study has suggested a "healthy migrant effect," with foreign-born Hispanics having lower mortality than native-born persons.[21] In that study, however, the Hispanic advantage remained even after adjusting for nativity.

The paradoxically low rates in Hispanics are made even more perplexing by the generally adverse cardiovascular risk profile in this racial-ethnic group.[28] On average, Hispanics have higher triglyceride levels, lower high-density-lipoprotein–cholesterol levels, higher systolic blood pressures, higher body mass index and central obesity, and a greater incidence and prevalence of non–insulin-dependent diabetes mellitus.[27,29–39] Among the racial-ethnic groups participating in the first National Health and Nutrition Examination Survey (NHANES-1) (1976–1980) and the Hispanic Health and Nutrition Examination Survey (HHANES) (1982–1984), Hispanics aged 45 to 74 years had the highest prevalence of diabetes mellitus (diagnosed plus undiagnosed): 12% in non-Hispanic whites, 19% in African Americans, and 24% in Mexican Americans.[40] Whereas the overall prevalence of hypertension is lower among Hispanics than among African Americans and similar to that of non-Hispanic whites,[27,32,41–43] the proportion of hypertensive persons with poor blood pressure control is high in both Hispanics and African American.[32,33,44] These adverse risk factors may be partially offset by a lower rate of smoking; in one study, California Hispanics were statistically less likely than non-Hispanic whites to be current smokers and, among smokers, smoked fewer cigarettes.[45] The recent BRFSS results also support a lower prevalence of current smoking in Hispanics, although significant only in women.

Vital-statistics studies and surveillance studies of incident and prevalent CVD have presented inconsistent findings with regard to the Hispanic paradox, especially for IHD. The Corpus Christi (Texas) Heart Project has shown a greater incidence of hospitalized myocardial infarction (MI) among Hispanics than among non-Hispanic whites.[28] This study, however, lacks data on silent MIs and fatal, out-of-hospital coronary events, which comprise a third to half of the fatal coronary events.[46]

The same study group also observed higher case-fatality rates after MI in Hispanics than in non-Hispanic whites.[10,47] In the San Luis Valley (Colorado). Diabetes Study, the prevalence of coronary heart disease in men with diabetes was 50% lower among Hispanics than non-Hispanic whites, but little difference was evident among those without diabetes.[48] In contrast to the San Luis study, the San Antonio (Texas) Heart Study showed a lower prevalence of MI in Hispanics than in non–Hispanic-white men in those without diabetes.[18] The higher case-fatality rate in Hispanics may explain the higher incidence of MI observed in one study and the lower prevalence observed in the other.[28,48] The lower IHD mortality observed in Hispanics in this and other vital-statistics studies, however, is not consistent with a concomitant high case-fatality and high incidence rate of MI previously reported for this racial-ethnic group.

Vital-statistics data have limitations that may explain these inconsistencies. We have not validated death certificate coding, and thus, coding artifacts could account for a portion of the observed racial-ethnic differences, especially for Hispanics. Substantial underreporting for Hispanic race or ethnicity has been noted in death certificates by some.[48,49] The National Longitudinal Mortality Study, however, observed that 94% of self-reported Hispanics were classified as Hispanic on the death certificate (98.7% overall agreement for Hispanic origin).[50] Inflating Hispanic rate numerators by an additional 6%, however, would not account for the sizable CVD rate discrepancies observed between Hispanics and African Americans or non-Hispanic whites. Previous studies have discounted coding artifacts because of the consistency in results across state borders.[33] Additional missed deaths could have resulted if Hispanics chose to return to Mexico or other countries of origin to die after severe CVD events and thus not be reported,[8] although this probably represents a small fraction of the total.

Alarmingly higher IHD and stroke mortality in African Americans than in non-Hispanic whites has resulted in a targeting of preventive efforts. Public health efforts to reduce the disparity in CVD outcomes require a continued identification and characterization of racial-ethnic and age-specific risks. It is important to evaluate not only group differences in mortality when considering possible target groups, but also current differences and secular trends in CVD risk factor profiles that affect future mortality. In recent years, the prevalences of cigarette smoking and obesity showed competing trends; the favorable decline in the prevalence of cigarette smoking in all sex-racial or -ethnic groups among California's adult population (27.5% decrease since 1984–1987) was offset by a dramatic rise in the prevalence of obesity (52.1% increase since 1984–1987). Between 1984 to 1987 and 1994 to 1996, the prevalence of a sedentary lifestyle was relatively stable at 55% for all Californians. Combined with the greater prevalence of diabetes in the minority populations, these are serious public health concerns with implications for future trends in CVD mortality. The effect of increasing levels of these risk factors on mortality trends may be somewhat offset by recent improvements in the management of patients at risk.

Clearly the forces behind the recent declines in CVD mortality have not benefited all demographic groups equally. The benefits of improved secondary prevention especially will likely lag for more economically disadvantaged groups. For African Americans, particularly early in life, the highest IHD and stroke mortality, lack of a comparable decline in age-adjusted IHD and stroke rates, and unfavorable trends in CVD risk factors suggest that increased primary and secondary prevention efforts should be focused on this race or ethnicity currently at greatest risk. Although comparing different populations requires caution, national data on IHD mortality from 1968 through 1985 indicate that the average annual percentage decline may be slowing dramatically for African-American women (−3.9% in 1968 to 1978, −2.0% in 1979 to 1985 in the national data,[4] and −0.3% in 1985 to 1991 in California data). A similar but more gradual decelerating decline occurred in African-American men and non-Hispanic white women, whereas an acceleration in the declines occurred in non-Hispanic white men. Despite the lower and declining age-adjusted IHD mortality, Hispanics had higher stroke mortality than non-Hispanic whites early in life. Taken together with Hispanics' less favorable CVD risk profile and the large number of Hispanics entering the ages of greater risk for IHD and stroke over the next several decades,[28] this minority population also deserves careful monitoring efforts. The interplay between race or ethnicity, risk factor profile, and the trends in CVD mortality and, in particular, the paradoxical finding of unexpectedly low CVD rates in Hispanics despite an adverse cardiovascular risk profile, lower socioeconomic status, and inconsistent epidemiologic findings need further investigation.

Acknowledgment

We thank David C. Goff, MD, PhD; Steven Haffner, MD, MPH; Joe V. Selby, MD; Steve Sidney, MD; and Patrick Fox, PhD, for their helpful comments on earlier versions of this manuscript.

REFERENCES

1. Cardiovascular disease surveillance, ischemic heart disease, 1980-1989. Atlanta (Ga): Centers for Disease Control and Prevention; 1993

2. Centers for Disease Control and Prevention. Trends in ischemic heart disease deaths—United States, 1990–1994. MMWR Morb Mortal Wkly Rep 1997; 46:146–150

3. Gillum RF, Sempos CT. The end of the long-term decline in stroke mortality in the United States? Stroke 1997; 28:1527–1529

4. Sempos C, Cooper R, Kovar MG, McMillen M. Divergence of recent trends in coronary mortality for the four major race-sex groups in the US. Am J Public Health 1988; 78:1422–1427

5. Williams DR, Collins C. US socioeconomic and racial differences in health: patterns and explanations. Annu Rev Sociol 1995; 21:349–386

6. Liao Y, Cooper RS. Continued adverse trends in CHD mortality among blacks, 1980–1991. Public Health Rep 1995; 110:572–579

7. Howard G, Anderson R, Sorlie P, Andrews V, Backlund E, Burke GL. Ethnic differences in stroke mortality between non-Hispanic whites, Hispanic whites, and blacks—the National Longitudinal Mortality Study. Stroke 1994; 25:2120–2125

8. Morgenstern LB, Spears WD, Goff DC Jr, Grotta JC, Nichaman MZ. African Americans and women have the highest stroke mortality in Texas. Stroke 1997; 28:15–18

9. Markides KS, Coreil J. The health of Hispanics in the southwestern United States: an epidemiologic paradox. Public Health Rep 1986; 101:253–265

10. Goff DC, Varas C, Ramsey DJ, Wear ML, Labarthe DR, Nichaman MZ. Mortality after hospitalization for myocardial infarction among Mexican Americans and non-Hispanic whites: the Corpus Christi Heart Project. Ethnicity Dis 1993; 3:55–63

11. Flegal KM, Ezzati TM, Harris MI, Haynes SG, Juarez RZ, Knowler WC, et al. Prevalence of diabetes in Mexican Americans, Cubans, and Puerto Ricans from the Hispanic Health and Nutrition Examination Survey, 1982–1984. Diabetes Care 1991; 14(suppl 3):628–638

12. International classification of diseases, 9th revision, clinical modification. Washington (DC): Public Health Service, US Dept of Health and Human Services; 1988

13. Fleiss JL. Statistical methods for rates and proportions, 2nd ed. New York (NY): John Wiley & Sons; 1981

14. Kleinman JC. State trends in infant mortality, 1968–83. Am J Public Health 1986; 76:681–687

15. Williams DR. Race and health: basic questions, emerging directions. Ann Epidemiol 1997; 7:322–333

16. Schoen R, Nelson VE. Mortality by cause among Spanish-surnamed Californians, 1969–71. Soc Sci Q 1981; 62:259–274

17. Goff DC, Ramsey DJ, Labarthe DR, Nichaman MZ. Acute myocardial infarction and coronary heart disease mortality among Mexican Americans and non-Hispanic whites in Texas, 1980 through 1989. Ethnicity Dis 1993; 3:64–69

18. Mitchell BD, Hazuda HP, Haffner SM, Patterson JK, Stern MP. Myocardial infarction in Mexican Americans and non-Hispanic whites: the San Antonio Heart Study. Circulation 1991; 83:45–51

19. Stern MP, Gaskill SP. Secular trends in ischemic heart disease and stroke mortality from 1970 to 1976 in Spanish-surnamed and other white individuals in Bexar County, Texas. Circulation 1978; 58:537–543

20. Stern MP, Bradshaw BS, Eifler CW, Fong DS, Hazuda HP, Rosenthal M. Secular decline in death rates due to ischemic heart disease in Mexican Americans and non-Hispanic whites in Texas, 1970–1980. Circulation 1987; 76:1245–1250

21. Sorlie PD, Backlund E, Johnson NJ, Rogot E. Mortality by Hispanic status in the United States. JAMA 1993; 270:2464–2468

22. Wing S. Social inequalities in the decline of coronary mortality. Am J Public Health 1988; 78:1415–1416

23. Wing S, Casper M, Riggan W, Hayes C, Tyroler HA. Socioenvironmental characteristics associated with the onset of decline of ischemic heart disease mortality in the United States. Am J Public Health 1988; 78:923–926

24. Kaplan GA, Keil JE. Socioeconomic factors and cardiovascular disease: a review of the literature. Circulation 1993; 88(pt 1):1973–1998

25. Council on Scientific Affairs, American Medical Association. Hispanic health in the United States. JAMA 1991; 265:248–252

26. Ginzburg E. Access to health care for Hispanics. JAMA 1991; 265:238–241

27. Health data summaries for California counties. Sacramento (Calif): Dept of Health Services, Planning and Data Analysis Section; 1994

28. Goff DC, Nichaman MZ, Chan W, Ramsey DJ, Labarthe DR, Ortiz C. Greater incidence of hospitalized myocardial infarction among Mexican Americans than non-Hispanic whites: the Corpus Christi Heart Project, 1988–1992. Circulation 1997; 95:1433–1440

29. Haffner SM, Stern MP, Hazuda HP, Pugh JA, Patterson JK. Hyperinsulinemia in a population at high risk for non-insulin dependent diabetes mellitus. N Engl J Med 1986; 315:220–224

30. Hamman RF, Marshall JA, Baxter J, Kahn LB, Mayer E, Orleans M, et al. Methods and prevalence of non-insulin dependent diabetes mellitus in a biethnic population: the San Luis Valley Diabetes Study. Am J Epidemiol 1989; 129:294–311

31. Haffner SM, Hazuda HP, Mitchell BD, Patterson JK. Increased incidence of type II diabetes mellitus in Mexican Americans. Diabetes Care 19091; 14:102–108

32. Haffner SM, Morales PA, Hazuda HP, Stern MP. Level of control of hypertension in Mexican Americans and non-Hispanic whites. Hypertension 1993; 21:83–88

33. Mitchell BD, Stern MP, Haffner SM, Hazuda HP, Patterson JK. Risk factors for cardiovascular disease mortality in Mexican Americans and non-Hispanic whites: the San Antonio Heart Study. Am J Epidemiol 1990; 131:423–433

34. Burchfield CM, Hamman RF, Marshall JA, Baxter J, Kahn LB, Amirani JJ. Cardiovascular risk factors and impaired glucose tolerance: the San Luis Valley Diabetes Study. Am J Epidemiol 1990; 131:57–70

35. Stern MP, Rosenthal M, Haffner SM, Hazuda HP, Franco LJ. Sex difference in the effects of sociocultural status on diabetes and cardiovascular risk factors in Mexican Americans: the San Antonio Heart Study. Am J Epidemiol 1984; 120:834–851

36. Diehl AK, Stern MP. Special health problems of Mexican Americans: obesity, gallbladder disease, diabetes mellitus, and cardiovascular disease. Adv Intern Med 1989; 34:79–96

37. Stern MP, Gaskill SP, Allen CR Jr, Garza V, Gonsales JL, Waldrop RH. Cardiovascular risk factors in Mexican Americans in Laredo, Texas: 1. Prevalence of overweight and diabetes and distributions of serum lipids. Am J Epidemiol 1981; 113:546–555

38. Stern MP, Haskell WL, Wood PD, Osann KE, King AB, Farquhar JW. Affluence and cardiovascular risk factors in Mexican-Americans and other whites in three northern California communities. J Chronic Dis 1975; 28:623–636

39. Stern MP, Gaskill SP, Hazuda HP, Gardner LI, Haffner SM. Does obesity explain excess prevalence of diabetes among Mexican Americans? results of the San Antonio Heart Study. Diabetologia 1983; 24:272–277

40. Kenny SJ, Aubert RE, Geiss LS. Prevalence and incidence of non-insulin-dependent diabetes. In: Diabetes in America. 2nd ed. Rockville (Md): National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health; 1995, NIH publication No. 95-1468

41. Franco LJ, Stern MP, Rosenthal M, Haffner SM, Hazuda HP, Comeaux PJ. Prevalence, detection, and control of hypertension in a biethnic community: the San Antonio Heart Study. Am J Epidemiol 1985; 121:684–696

42. Haffner SM, Mitchell BD, Stern MP, Hazuda HP, Patterson JK. Decreased prevalence of hypertension in Mexican Americans. Hypertension 1990; 16:225–232

43. Haffner SM, Mitchell BD, Valdez RA, Hazuda HP, Morales PA, Stern MP. Eight-year incidence of hypertension in Mexican Americans and non-Hispanic whites: the San Antonio Heart Study. Am J Hypertens 1992; 5:147–153

44. 1988 Joint National Committee. The 1988 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med 1988; 148:1023–1028

45. Winkleby MA, Schooler C, Kraemer HC, Lin J, Fortman SP. Hispanic versus white smoking patterns by sex and level of education. Am J Epidemiol 1995; 142:410–418

46. Escobedo LG, Caspersen CJ. Risk factors for sudden coronary death in the United States. Epidemiology 1997; 8:175–180

47. Goff DC, Ramsey DJ, Labarthe DR, Nichaman MZ. Greater case-fatality after myocardial infarction among Mexican Americans and women than among non-Hispanic whites and men: the Corpus Christi Heart Project. Am J Epidemiol 1994; 139:474–483

48. Rewers M, Shetterly SMN, Hoag S, Baxter J, Marshall J, Hamman RF. Is the risk of coronary heart disease lower in Hispanics than in non-Hispanic whites? the San Luis Valley Diabetes Study. Ethnicity Dis 1993; 3:44–54

49. Poe GS, Powell-Griner E, McLaughlin JK, Placek PJ, Thompson GB, Robinson K. Comparability of the death certificate and the 1986 National Mortality Followback Survey. Vital Health Stat 2 1993; 118:1–53

50. Sorlie PD, Rogot E, Johnson NJ. Validity of demographic characteristics on the death certificate. Epidemiology 1992; 3:181–184

Articles

Failure of Physician Documentation of Sleep Complaints in Hospitalized Patients

HORST-HELMUT MEISSNER, MD; ANN RIEMER; SILVERIO M. SANTIAGO, MD; MYRON STEIN, MD; MICHAEL D. GOLDMAN, MD, ScD; *and* ADRIAN J. WILLIAMS, MB, *Los Angeles, California*

Sleep disorders are acknowledged to be common but remain underrecognized by the medical community, often attributed to the failure to question patients about their sleep quality. We examined the prevalence of sleep complaints (insomnia or excessive daytime sleepiness) in a group of general medical patients by administering a questionnaire to hospitalized patients in a Veterans Affairs tertiary care medical center. A total of 222 consecutive adults (215 men, 60 ± 14 years; body mass index, 24.8 ± 5.6) completed the questionnaire. Of these, 105 patients (47%) had either insomnia, excessive daytime somnolence, or both; 63 (28%) had excessive daytime somnolence, which was severe in 27 (12%). Of 75 patients (34%) who had insomnia, a third were taking hypnotic medication. Forty patients (18%) had snoring, which was associated with excessive daytime somnolence in 36, whereas 46 patients (21%) had either restless legs or a combination of leg jerks and leg kicking or twitching during sleep, associated with a sleep complaint (insomnia in 32). The medical records were subsequently reviewed to assess the admitting physicians' recognition of these symptoms. No record included mention of any patient symptom related to sleep. We conclude that symptoms related to sleep, some of which may be clinically important, are common, and that none of these complaints appear to be recognized by the physicians of record.

(Meissner HH, Riemer A, Santiago SM, Stein M, Goldman MD, Williams AJ. Failure of physician documentation of sleep complaints in hospitalized patients. West J Med 1998; 169:146–149)

The frequent occurrence of sleep disorders in our society is increasingly reported, and this fact has been stressed in the summary statement of the National Commission on Sleep Disorders.[1] About 40 million Americans suffer from chronic sleep disorders, and an additional 20 to 30 million have intermittent sleep-related problems.[1] The costs of sleep-related problems are in the tens of billions of dollars and include sleep-related tragedies such as the Exxon *Valdez* grounding and the Challenger space shuttle disaster.[1] Despite this pervasive adverse effect on our society, sleep-related problems have had little recognition as a public health issue, in part because of the lack of training in this area for health care professionals.

We undertook the present study to evaluate the frequency and severity of sleep complaints and possible sleep-related problems in patients admitted to the general medical service of a Veterans Affairs tertiary care medical center by surveying consecutive admissions independent of (that is, without the knowledge of) the house-staff physicians caring for these patients. At the same time, we assessed patients' medical histories, as recorded by the admitting physicians, with respect to mention of these symptoms and sleep-related problems by reviewing the medical admission notes.

Patients and Methods

We used a standardized sleep disorders center questionnaire (Figure 1) routinely administered to all patients being evaluated for possible sleep disorders in the pulmonary and critical care medicine section to survey newly admitted patients. This survey instrument was intended to assess sleep-related issues as unobtrusively as possible to obtain maximal patient cooperation and, accordingly, was limited to one page. The questionnaire was given to 232 patients admitted to the medical service during two sepa-

From the Medical and Research Services, West Los Angeles Department of Veterans Affairs (VA) Medical Center (Drs Meissner and Riemer), and the Department of Medicine (Drs Riemer, Santiago, Stein, and Goldman), UCLA School of Medicine, Los Angeles, Calif, and Lane Fox Respiratory Unit (Dr Williams), St Thomas' Hospital, London, England.

Reprint requests to Horst-Helmut Meissner, MD, Pulmonary and Critical Care Medicine, 111Q, West Los Angeles VA Medical Center, 11301 Wilshire Blvd, Los Angeles, CA 90073.

ABBREVIATIONS USED IN TEXT
AIDS = acquired immunodeficiency syndrome
EDS = excessive daytime somnolence
HIV = human immunodeficiency virus

rate one-month periods. Patients in most cases were admitted with subacute exacerbations of chronic multiple organ system diseases. They were instructed to respond to questions with respect to their usual state of health (specifically not limited to the time immediately preceding admission) and were allowed one day to complete the questionnaire on their own. At the time of collection, clarification of the questionnaire was offered by one of the investigators. Clarification reemphasized, in particular, issues of chronicity of any symptoms and stressed that the patients' responses should apply to their usual habits.

From the responses to the questionnaire, we identified sleep symptoms as follows: excessive daytime sleepiness (EDS) was defined as excessive sleepiness during the day in association with another sleep complaint such as snoring, restless legs, or the use of hypnotic agents. It was considered severe if sleeping spells occurred while driving an automobile. Insomnia was defined as complaints of difficulty in both initiating and maintaining sleep, or either complaint associated with the routine use of hypnotics. A clinically important complaint of restless legs was defined as the complaint of restless legs[2] or both limb jerking and kicking or twitching during sleep, when these last complaints were associated with insomnia or excessive sleepiness. Similarly, snoring was defined only if associated with insomnia or EDS and not as a solitary finding.

Results

In all, 232 patients were asked to participate in the survey, 10 of whom refused participation. A total of 222 completed questionnaires were obtained from 215 men and 7 women. The ages of patients ranged from 22 to 99 years, with a mean age of 60 ± 14 years (±SD). Patients' weight averaged 80 ± 43 kg (mean ± SD). Patients' body mass index (weight in kilograms divided by height in meters^2) averaged 24.8 ± 5.8 (mean ± SD). Alcohol consumption was admitted to be regular in 47 of 222 patients.

Virtually all patients had multiple organ system disease. Of 74 patients with cardiovascular diagnoses (unstable angina, possible myocardial infarction, cardiac dysrhythmia or congestive heart failure [or both], dilated cardiomyopathy, or peripheral vascular disease), 40 were admitted for this problem. Of 63 patients with malignant

Date: _____ **Name:** _____
Age: _____ Phone #: _____
Weight: _____ Height: _____
Usual bedtime: ____ Usual awakening time: _____
Usual awakening time on weekends: _____
Shirt collar size: __
Medications: _____
Please circle:

Y	N	Use tobacco (how much? _____)
Y	N	Use alcohol (how much? _____)
Y	N	Loud snorer
Y	N	Stop breathing during sleep
Y	N	Choking/gasping during sleep
Y	N	Waking up refreshed
Y	N	Waking up with a headache
Y	N	Fall asleep during the day in quiet surrounding
Y	N	Driving accident or near accident due to sleeping
Y	N	Tired or fatigued during usual daytime activity
Y	N	Kicking or twitching during sleep
Y	N	Legs jerk during sleep
Y	N	Experience restlessness, tingling, crawling in legs
Y	N	Trouble falling asleep (for how long? _____)
Y	N	Trouble returning to sleep (for how long? _____)
Y	N	Use sleeping pills (for how long? _____)
Y	N	Experience weakness of arms or legs when emotional
Y	N	Experience inability to move when waking up

Figure 1.—This questionnaire was administered to patients to assess the prevalence of sleep complaints.

TABLE 1.—*Results of Sleep Complaints Questionnaire Administered to 222 Patients*

Result	*No.*	*(%)*
Questionnaires administered	222	
Positive for EDS and/or insomnia	105	(47)
Positive for EDS (with or without insomnia)	63	(28)
EDS with motor vehicle accident	27	(12)
Positive for insomnia (with or without EDS)	75	(33)
Insomnia with hypnotic use	25	(11)
Snoring with EDS and/or insomnia	40	(18)
Restless legs with EDS and/or insomnia	46	(20)

EDS = excessive daytime somnolence

disease, 24 were admitted for the assessment of metastases or suspicious masses. Neurologic signs and symptoms, including severe headaches, seizures, loss of consciousness, falls or weaknesses, and multiple sclerosis, were the cause of admission in 51 patients. Of 45 patients with diabetes mellitus, 17 were admitted because of either a new onset of diabetes mellitus or poor control. Of 26 patients with chronic obstructive lung disease, 16 were admitted for an exacerbation. Thirty-two patients had renal disease, of whom 11 had chronic renal failure. Of 26 patients with drug or alcohol abuse, 15 were admitted because of the need for control. Sixteen patients were seropositive for the human immunodeficiency virus (HIV), of whom 9 were admitted for complications of the acquired immunodeficiency syndrome (AIDS). In all, 26 patients had gastrointestinal system diseases, of whom 12 were admitted to assess pancreatitis, jaundice, ascites, melena, or upper gastrointestinal bleeding.

Table 1 summarizes questionnaire responses. Almost half of the surveyed patients had a sleep complaint. Insomnia was noted by a third of the patients and, of these, 25 were currently taking hypnotic drugs. More than a fourth of all patients had daytime sleepiness. Severe EDS, that is, sleepiness that included episodes of falling asleep while driving, occurred in 27 patients (43%) of those with EDS, or 12% of all patients surveyed. Thus, at least 23% of this population probably had a clinically substantial sleep complaint (25 insomniacs taking hypnotic medications regularly and 27 with EDS sleepy enough to have fallen asleep while driving).

The medical records of all patients were reviewed by one of us (HHM) following the administration of the questionnaire. This was done independent of analyses of questionnaire responses. For no patient was any record made by the house-staff physicians of questions asked related to sleep. No medical record included mention of any patients' symptoms related to sleep.

Discussion

This study has two important findings: First, symptoms related to sleep are common and, in almost a fourth of admissions to a general medical service, may be clinically substantial. Second, none of the patients' sleep-related symptoms appear to be recognized by the physicians caring for the patients.

These findings are not surprising in the group studied. The group was unwell and, as such, liable to more sleep symptoms than normal.[3] Their disease severity was in general pronounced, but all were admitted to the general medical wards and none to the intensive care unit,[4] including the 19% of patients with either HIV infection or AIDS or alcohol or drug abuse. A substantial number of the patients with cancer had metastatic disease, and a third of the patients with diabetes mellitus had chronic renal failure. Most of the patients with cardiovascular disease had hypertension, and many of the patients admitted for neurologic disease had hypertension, chronic lung disease, or urinary tract disease. Thus, the finding that half of these patients had sleep complaints is not surprising.

Because of the coexistence of multiple organ system disease and the relatively small percentage of patients with respiratory disease, we were unable to obtain a significant correlation between respiratory tract symptoms and sleep complaints.[5] Similarly, the few women subjects preclude any useful comparisons among their diagnoses and sleep complaints or between men and women in this population. The five patients with multiple sclerosis had sleep symptoms comparable with those of other patients with neurologic diagnoses, although from the limited data we obtained in this questionnaire, we were unable to examine the likelihood of their disease contributing to specific sleep-disordered symptoms.[6–8] Patients with HIV infection or AIDS and chronic renal failure had a higher prevalence of sleep symptoms.[7,9] Of 16 patients admitted with AIDS, 11 had substantial sleep complaints, but only 1 had severe EDS. Of 11 patients admitted for chronic renal failure, 6 had substantial sleep complaints, of whom 2 had severe EDS. Finally, we did not observe the patients' hospital course because this study was limited to a comparison of questionnaire responses with admitting house-staff medical history taking.

We took great care to emphasize to all patients that we sought responses to their usual habits, specifically not associated with the circumstances that led to their present admission. That none of the patients brought these symptoms up spontaneously to the admitting physician is also not surprising.[10] That the admitting physician did not initiate questioning concerning sleep habits is also consistent with the findings of other studies.[10,11]

Our conclusions regarding sleep complaints are based on conservative estimates of the likelihood of clinical relevance. With respect to restless legs and sleep disturbances associated with leg movements, although leg movements may be physiologic hypnic jerks, we tried to minimize ambiguity by requiring both kicking and twitching movements in association with complaints of insomnia or EDS, to define a clinically meaningful symptom. The symptoms of EDS or insomnia were

meaningful to the patients. These were judged medically important if associated with other conditions suggesting probable sleep disorders (hypnotic medication use or another sleep disorder such as snoring or restless legs). In the case of EDS, sleeping spells that occur specifically while driving constitute a severe problem. Other instances of such "active" sleepiness, for example, during conversations, were not sought. This study largely involved male patients, who would be more prone to sleep apnea,[12] whereas female patients are more prone to insomnia.[13] Nevertheless, the insomnia rate in the present survey was remarkably similar to that reported in other sample groups,[14,15] possibly reflecting the effect of coexisting multiple organ system disease.

Finally, we accept the limitation of this study that the diagnostic importance of positive responses to questionnaires has not been quantified by objective documentation of nocturnal sleep. This study was not intended to establish a diagnosis of sleep disorders, but, rather, to survey hospitalized patients concerning their sleep habits.

The absence of any recognition of these complaints in the medical record is consistent with previous reports. In a survey of 10,000 medical records from five general practices in California with an average of five visits per record (50,000 patient contacts), sleep was mentioned only 123 times. In none of these records was a physician's response judged to be adequate by the reviewer.[1] A survey of 10 million diagnoses of the *International Classification of Diseases* revealed only 73 cases of sleep apnea, whereas 100,000 would be predicted based on a prevalence of only 1%.[1] Finally, a review of 2 million death certificates in the United States in 1988 revealed only 3 cases in which a sleep disorder was mentioned as the primary diagnosis and another 49 in which a sleep disorder was listed as a secondary factor.[1]

Why are sleep-related disorders so underrecognized by the medical profession? Part of the answer undoubtedly lies in the traditional pattern of medical education. The report of Rosen and co-workers highlights the limitations of didactic teaching, with less than 5% of medical schools in the United States providing more than four hours of such teaching.[11] In addition, textbooks concerned with physical diagnosis and the taking of medical histories mention sleep little, if at all. In some modern texts, sleep is relegated to the end of the review of systems with no qualifying statements[16] or to "habits," with little breadth or depth to the questions.[17] These circumstances suggest that physicians involved in sleep disorders medicine need to assume the responsibility of contributing to medical education as well as providing patient care services. Contributions can be usefully integrated into medical student and postgraduate teaching at several levels. Students can be introduced to sleep-related problems in physiology, physical diagnosis skills, and general medical clinical rotations. At the postgraduate levels, specialty rotations in pulmonary medicine, gerontology, neurology, psychiatry, and cardiology can usefully include patients with sleep-related disorders.

REFERENCES

1. Report of the National Commission on Sleep Disorders Research. Vol 1. Executive summary and executive report. Bethesda (Md): National Institutes of Health; 1992

2. Diagnostic Classification Steering Committee, MJ Thorpy, Chair. International classification of sleep disorders: diagnostic and coding manual. Rochester (Minn): American Sleep Disorders Association; 1990

3. Dicicco BS, Cooper JN, Waldhorn R. Sleep disorders in medical illness. Psychiatr Med 1986; 4:133–148

4. Edwards GB, Schuring LM. Pilot study: validating staff nurses' observations of sleep and wake states among critically ill patients, using polysomnography. Am J Crit Care 1993; 2:125–131

5. Klink ME, Dodge R, Quan SF. The relation of sleep complaints to respiratory symptoms in a general population. Chest 1994; 105:151–154

6. Taphoorn MJ, van Someren E, Snoek FJ, Strijers RL, Swaab DF, Visscher F, et al. Fatigue, sleep disturbances and circadian rhythm in multiple sclerosis. J Neurol 1993; 240:446–448

7. Devins GM, Edworthy SM, Paul LC, Mandin H, Seland TP, Klein G, et al. Restless sleep, illness intrusiveness, and depressive symptoms in three chronic illness conditions: rheumatoid arthritis, end-stage renal disease, and multiple sclerosis. J Psychosom Res 1993; 37:163–170

8. Clark CM, Fleming JA, Li D, Oger J, Klonoff H, Paty D. Sleep disturbance, depression, and lesion site in patients with multiple sclerosis. Arch Neurol 1992; 49:641–643

9. Darko DF, McCutchan JA, Kripke DF, Grillin JC, Golshan S. Fatigue, sleep disturbance, disability and indices of progression of HIV infection. Am J Psychiatry 1992; 149:514–520

10. Sleep in America: a national survey of US adults. Princeton (NJ): The Gallup Organization; 1995

11. Rosen RC, Rosekind M, Rosevear C, Cole WE, Dement WC. Physician education in sleep and sleep disorders: a national survey of US medical schools. Sleep 1993; 16:249–254

12. Young T, Palta M, Dempsey JA, Skatrud JB, Weber S, Badr S. The occurrence of sleep disordered breathing among middle-aged adults. N Engl J Med 1993; 328:1230–1235

13. Hauri P, Fisher J. Persistent psychophysiologic (learned) insomnia. Sleep 1986; 9:38–53

14. Mellinger GD, Balter MB, Uhlenhuth EH. Insomnia and its treatment. Arch Gen Psychiatry 1985; 42:225–232

15. Sleep in America: a national survey of US adults. Princeton (NJ): The Gallup Organization; 1991

16. Seidel HM, Ball JW, Dains JE, Benedict GW. Mosby's guide to physical examination. 2nd ed. St Louis (Mo): Mosby Year Book; 1991

17. Bates B. A guide to physical examination and history taking. 4th ed. Philadelphia (Pa): JB Lippincott; 1987

Articles

Effect of Mammography Outreach in Women Veterans

KATHIE M. DALESSANDRI, MD; MELISSA COOPER, RN; *and* TUMAINI RUCKER, *Palo Alto, California*

We undertook this study to test whether progressive intervention would increase the use of mammography. In 1995, we randomly assigned into 2 groups 717 underserved women veterans in the Veterans Affairs Palo Alto (California) Health Care System (VAPAHCS) who earned less than $22,000 a year. The women were sent an informational letter and brochure explaining why mammography is needed and how often. The letter further requested that if the woman was due for a screening mammogram or if a lump or other recent change in her breast had occurred, that she call for scheduling of a free mammogram and a visit to the breast clinic. Women in group I (n = 351) received no further intervention. Women in group II (n = 366) received a follow-up phone call by a breast care nurse if they had not responded within 45 days of the informational mailing. The nurse talked to each woman about her particular needs, explained to her that the screening mammogram would be provided free of charge, and discussed transportation arrangements to the mammography facility. A total of 17 women in group I had mammograms versus 100 in group II during the same time period. We conclude that the additional intervention of a phone call by a breast care nurse increased use by more than 5-fold, which reached significance ($P < .01$).

(Dalessandri KM, Cooper M, Rucker T. Effect of mammography outreach in women veterans. West J Med 1998; 169:150–152)

The purpose of this study was to evaluate whether progressive intervention by the mailing of an informational brochure and letter, followed by a phone call by a breast care nurse, would increase the use of mammography in underserved women veterans. Underserved women veterans are defined as those who earn less than $22,000 a year, making them eligible for free mammograms. Women veterans in 1995 made up 4.6% of the total veteran population, and this percentage is increasing as more women enlist in the active-duty military force.[1] Although traditionally most of the veterans services have catered to men, the Department of Veterans Affairs (VA) has become more sensitive to the needs of women and has arranged for mammography services in or near veterans health care facilities. For this service to be used, an outreach program was designed and its effectiveness analyzed.

Subjects and Methods

A total of 717 women veterans in the VAPAHCS who were eligible for free mammograms were randomly assigned into two groups based on even and odd endings of their social security number. Women in group I (n = 351) were sent an informational brochure explaining the need for screening mammography and recommendations for how often it should be done. A letter was included with the brochure that instructed the women that if they were due for their screening mammogram or had felt a lump or other recent change in their breast, they should call for the scheduling of a free mammogram. No further intervention was provided to group I women. Women in group II (n = 366) received, in addition to the initial mailing, a phone call by the breast care nurse if they had not responded to the mailing within 45 days. The breast care nurse talked to each woman about her particular needs and explained that the screening mammogram would be provided free of charge. The nurse assisted with the scheduling of a mammogram and answered any questions regarding transportation to the mammography facility. Each phone call took about 15 minutes, which amounted to about 92 hours, or 0.04 full-time-equivalent, of a registered nurse's time. Patients who had moved or died were not included in the study.

Demographic information gathered included age, branch of service, marital status, race, and employment status. This study was performed over a six-month period. Approval was obtained from the institutional review

From the Veterans Affairs Palo Alto Health Care System (VAPAHCS) (Dr Dalessandri and Ms Cooper), Palo Alto, and the Department of Surgery, Stanford University School of Medicine (Dr Dalessandri), Stanford, California. Ms Rucker is a 3rd-year student at Stanford University.

Reprint requests to Kathie M. Dalessandri, MD, Department of Surgery (112), VAPAHCS, 3801 Miranda Ave, Palo Alto, CA 94304.

TABLE 1.—*Demographic Characteristics for Women in Groups I and II*

Characteristics	*Group I (n = 351), %*	*Group II (n = 366), %*
Age, yr		
<40	28	29
40-49	22	19
50-59	9	14
60-69	12	11
70-79	23	24
≥80	7	7
Marital status		
Married	24	25
Unmarried or widowed	66	69
Employment status		
Employed	24	20
Unemployed	58	62
Not listed	18	22
Race		
White	48	57
Nonwhite	10	10
Not listed	42	37
Branch of service		
Army	48	54
Navy	25	25
Coast Guard	3	1
Air Force	14	12
Marine Corps	4	6
Not listed	6	6

board of the VA Health Care System. The χ^2 test was used for statistical analysis.

Results

A total of 17 patients in group I versus 100 patients in group II received mammograms during the same time period. This finding reached significance ($P < .01$). Demographic characteristics of the two groups were similar (Table 1).

Discussion

National health promotion and disease prevention objectives are major goals for "Healthy People 2000."[2] Mortality from breast cancer can be reduced by 34%[3,4] by the use of regular mammograms, yet there are barriers that decrease their use. Approximately 50% of American women do not receive regular mammograms, with variation depending largely on their age and insurance coverage.[5–9] Some of the barriers to regular mammography include cost,[6,10] a lack of referral by a health care professional,[11–15] and a lack of general education about breast cancer and mammography.[16–19] In this case, the cost factor was removed because the mammograms were provided free of charge. General education brochures outlining the current recommendations by the American Cancer Society were sent to all 717 women veterans. The primary difference between the two groups was the personal input from the breast care nurse, who called each woman in group II and facilitated the care of the patient by the scheduling of a mammogram and by answering any questions the woman might have regarding her mammogram. The result was a fivefold improvement in mammography use over a six-month period in 1995.

In a health maintenance organization membership, it was found that telephone counseling nearly doubled the odds of a woman getting a mammogram.[20] In our underserved women veterans, the results were even more remarkable. This appears to be a powerful intervention that could be applicable to other forms of preventive screening measures as well. Screening mammography causes a dramatic shift of the detection of breast cancer from a later to an earlier stage.[21–23] There is a 50% decrease in mortality and a substantial decrease in treatment costs,[22] with estimated savings of about $9,700 per case of cancer found in underserved persons.[23]

Acknowledgment

This work was supported in part by a grant from the VA Health Services Research and Development Grant. Special thanks go to Kelvin Lee, PhD Biostatistics, of the Palo Alto VA statistics department, who helped analyze the data.

REFERENCES

1. Rahman A. Profile of women treated at VA medical centers during fiscal year 1995. Veterans Health System Q 1997 Jan, pp 34–38

2. Healthy People 2000. National Health Promotion and Disease Prevention Objectives. Washington (DC): US Dept of Health and Human Services; 1991, DHHS publication PHS 91-50213

3. Elwood JM, Cox B, Richardson AK. The effectiveness of breast cancer screening by mammography in younger women. Online J Curr Clin Trials [serial online] 1993 Feb; 24:doc 32

4. Shapiro S, Venet W, Strax P, Venet L, Roeser R. Selections, follow-up, and analysis in the Health Insurance Plan study: a randomized trial with breast cancer screening. Monogr Natl Cancer Inst 1985; 67:65–67

5. National Cancer Institute Breast Cancer Screening Consortium. Screening mammography: a missed clinical opportunity? results of the NCI Breast Cancer Screening Consortium and National Health Interview Survey studies. JAMA 1990; 264:54–58

6. Zapka JG, Hosmer D, Costanza ME, Harris DR, Stoddard A. Changes in mammography use: economic, need, and service factors. Am J Public Health 1992; 82:1345–1351

7. Zapka JG. Promoting participation in breast cancer screening. Am J Public Health 1994; 84:12–13

8. Breen N, Kessler L. Changes in the use of screening mammography: evidence from the 1987 and 1990 National Health Interview surveys. Am J Public Health 1994; 84:62–67

9. Blustein J. Medicare coverage, supplemental insurance, and the use of mammography by older women. N Engl J Med 1995; 332:1138–1143

10. Urban N, Anderson G, Peacock S. Mammography screening: how important is cost as a barrier to use? Am J Public Health 1994; 84:50–55

11. Fox SA, Murata PJ, Stein JA. The impact of physician compliance on screening mammography for older women. Arch Intern Med 1991; 151:50–56

12. Iverson DC. Involving providers and patients in cancer control and prevention efforts—Barriers to overcome. Cancer 1993; 72(suppl):1138–1143

13. Costanza ME, Zapka JG, Harris DR, Hosmer D, Barth R, Gaw VP, et al. Impact of a physician intervention program to increase breast cancer screening. Cancer Epidemiol Biomarkers Prev 1992; 1:581–589

14. Mayer T, Bartholomew S, Clapp E, Elder J. Facility-based inreach strategies to promote annual mammograms. Am J Prev Med 1994; 10:353–356

15. McCarthy B, MacWilliam C, Yood M, Lee M. Screening mammography use: the importance of a population perspective. Am J Prev Med 1996; 12:91–95

16. Rimer BK, Resch N, King E, Ross E, Lerman C, Boyce A, et al. Multistrategy health education program to increase mammography use among women ages 65 and older. Public Health Rep 1992; 107:369–380

17. Rimer BK. Improving the use of cancer screening for older women. Cancer 1993; 72(3 Suppl):1084–1087

18. Crooks CE, Jones SD. Educating women about the importance of breast screenings: the nurse's role. Cancer Nurs 1989; 12:161–164

19. Nielsen CC. Women's use of mammographic screening: the role of information, cues, and reinforcement. Conn Med 1990; 54:374–347

20. King EU, Rimer BK, Seay J, Balshem A, Engstrom P. Promoting mammography use through progressive interventions: is it effective? Am J Public Health 1994; 84:104–106

21. McCoy CB, Smith SA, Metsch LR, Anwyl RS, Correa R, Bankson L, et al. Breast cancer screening of the medically underserved: results and implications. Cancer Pract 1994; 2:267–274

22. Zavertnik JJ, McCoy CB, Robinson DS, Love N. Cost-effective management of breast cancer. Cancer 1992; (suppl):1979–1984

23. Zavertnik JJ. Strategies for reaching poor blacks and Hispanics in Dade County, Florida. Cancer 1993; 72(suppl):1088–1092

Use of and Interest in Alternative Therapies Among Adult Primary Care Clinicians and Adult Members in a Large Health Maintenance Organization

NANCY P. GORDON, ScD; DAVID S. SOBEL, MD, MPH; *and* ELFI Z. TARAZONA, MPH, *Oakland, California*

During spring 1996, random samples of adult primary care physicians, obstetrics-gynecology physicians and nurse practitioners, and adult members of a large northern California group practice model health maintenance organization (HMO) were surveyed by mail to assess the use of alternative therapies and the extent of interest in having them incorporated into HMO-delivered care. Sixty-one percent (n = 624) of adult primary care physicians, 70% (n = 157) of obstetrics-gynecology clinicians, and 50% (2 surveys, n = 1,507 and n = 17,735) of adult HMO members responded. During the previous 12 months, 25% of adults reported using and nearly 90% of adult primary care physicians and obstetrics-gynecology clinicians reported recommending at least 1 alternative therapy, primarily for pain management. Chiropractic, acupuncture, massage, and behavioral medicine techniques such as meditation and relaxation training were most often cited. Obstetrics-gynecology clinicians used herbal and homeopathic medicines more often than adult primary care physicians, primarily for menopause and premenstrual syndrome. Two thirds of adult primary care physicians and three fourths of obstetrics-gynecology clinicians were at least moderately interested in using alternative therapies with patients, and nearly 70% of young and middle-aged adult and half of senior adult members were interested in having alternative therapies incorporated into their health care. Adult primary care physicians and members were more interested in having the HMO cover manipulative and behavioral medicine therapies than homeopathic or herbal medicines.

(Gordon NP, Sobel DS, Tarazona EZ. Use of and interest in alternative therapies among adult primary care clinicians and adult members in a large health maintenance organization. West J Med 1998; 169:153–161)

Alternative, unconventional, or complementary therapies have been defined as medical practices that are not in conformity with the standards of the western medical community (for example, they are not widely taught at medical schools, generally available at hospitals, or subject to reimbursement).[1] Alternative therapies are frequently used by patients with cancer,[2–7] arthritis,[8,9] chronic back pain,[10–12] human immunodeficiency virus infection or the acquired immunodeficiency syndrome,[13] and gastrointestinal problems.[14,15] Population-based surveys conducted in the 1990s suggest that substantial proportions of the populations of the United States and western Europe have been using alternative therapies in addition to conventional western medicine.[12,16–19] Furthermore, surveys in the Netherlands, Belgium, and the United Kingdom have found that more than half the public would like to have coverage for some forms of alternative therapies.[18]

There is also evidence that a substantial number of traditionally trained health care professionals are incorporating alternative therapies into their patient care or are interested in doing so. Recent surveys of general practitioners in western Europe, Israel, and former Commonwealth nations have found that from 25% to more than 80% of general practitioners are using alternative or complementary methods to supplement mainstream medicine, and most feel that these therapies include ideas and methods from which "regular" medicine might benefit.[20–28] Alternative therapies also appear to be gaining acceptance among the health care community in the United States. A 1992 survey of community physicians in Washington State and New Mexico found that more than 60% had referred at least one patient for alternative therapy in the past year, 12% incorporated alternative techniques into their practice, and 42% had used alternative therapies for themselves or family members (or

From the Division of Research (Dr Gordon and Ms Tarazona) and the Department of Regional Health Education (Dr Sobel), Kaiser Permanente Medical Care Program (Northern California Region), Oakland, California.

This research was supported in part by funds from the Innovation Program and the Community Services Program of Kaiser Permanente's Northern California Region.

Reprint requests to Nancy P. Gordon, ScD, Division of Research, Kaiser Permanente Medical Care Program, 3505 Broadway, Oakland, CA 94611 (e-mail: npg@dor.kaiser.org).

ABBREVIATIONS USED IN TEXT

HMO = health maintenance organization
PMS = premenstrual syndrome

both). Primary care physicians were more likely than specialists to make referrals for alternative therapies.[29] A survey of family physicians in the Chesapeake Bay region found that most considered many alternative therapies to be effective and had referred patients to alternative practitioners or used these therapies in their own practice.[30] A survey of family practitioners in Washington State found that nearly 60% had encouraged their patients to seek chiropractic care.[31] An Office of Alternative Medicine has been established at the National Institutes of Health to investigate the effectiveness of various alternative modalities and act as an information clearinghouse, several professional journals devoted to alternative medicine have recently been started, and a growing number of medical schools and centers have developed programs for the study of alternative therapies. Many health insurance companies now routinely cover chiropractic care, some pay for acupuncture, and others are covering naturopathy, reflexology, and other unconventional practices.[32]

In the context of growing interest in alternative therapies among both patients and health care professionals, in 1996 we surveyed adult primary care physicians, obstetrics-gynecology physicians and nurse practitioners, and adult health plan members of the Kaiser Permanente Medical Care Program, Northern California, a large group practice health maintenance organization (HMO), to learn what alternative therapies clinicians were recommending to members for the treatment of health conditions, which therapies members were using, and which alternative therapies both constituencies were interested in having the HMO offer as a covered benefit.

Methods

During the spring of 1996, questionnaires were sent to 1,027 physicians who practiced at least 50% time in a department of adult primary care medicine and a random sample of 225 obstetrics-gynecology physicians and nurse practitioners at the 32 Kaiser Permanente medical facilities in northern California. Obstetrics-gynecology clinicians were included in the study because they frequently provide all primary care for some women and provide care for gynecologic conditions such as premenstrual syndrome (PMS) and menopausal symptoms. Concurrently, a stratified random sample of approximately 3,000 adult health plan members were surveyed. Both surveys had the stated goal of learning about prior use of alternative therapies and the opinions about whether the HMO should incorporate alternative therapies into its health care delivery system to inform decisions about future HMO services. At about the same time, a large-scale general member health survey that collected a wide range of information related to health, health care use, and sociodemographic characteristics and that included 1 multi-item question about alternative therapies was also being conducted with a stratified random sample of adult health plan members (n = 34,000). Data from this larger member survey were used to estimate the proportions of adult members who had used the 20 alternative therapies ever and in the past 12 months.

In all three surveys, as many as three attempts were made to obtain completed questionnaires. Phone follow-up interviews of random samples of nonrespondents to the alternative therapy surveys were used to determine possible response bias. Because adult members were nonproportionally sampled from six age-sex strata and response rates differed significantly across strata, respondents to the member surveys were assigned weights based on their age and sex so that the final sample used for the analyses would better reflect the actual age-sex composition of the adult health plan membership rather than that of the respondent sample.

To estimate the prevalence of alternative therapy use, clinicians and members were asked to indicate which of the following 20 alternative therapies they had used to treat or prevent health problems: chiropractic, osteopathy, acupuncture, acupressure, massage therapy, body work, biofeedback, hypnosis or self-hypnosis, meditation or mindfulness, visualization or guided imagery, relaxation training, homeopathic remedies, herbal remedies, megavitamin therapy, special diet, religious healing or prayer, psychological counseling, yoga, tai chi or *chi gong*, and support groups or 12-Step programs. Brief descriptions of these alternative therapies were provided in the questionnaires. Clinicians were asked whether they had used or recommended the therapies to patients during the past 12 months, and members were asked whether they had ever used the therapies and whether the use was during the past 12 months. Both clinicians and members were asked to list the health conditions for which these therapies had been used.

χ^2 tests were used to assess whether differences in proportions—for example, percentages of adult primary care physicians versus obstetrics-gynecology clinicians or young or middle-aged adults versus adults aged 65 years or older reporting the use of different therapies—were statistically significant. Pearson correlations and multiple linear regression were used to assess significance of differences between groups with regard to continuous variables, such as the level of interest.

Results

Clinician Survey

About 61% (n = 624) of adult medicine primary care physicians and 70.4% (n = 157) of obstetrics-gynecology physicians and nurse practitioners responded to the survey. The characteristics of the respondent sample are shown in Table 1. The results of a survey of a random sample of physician nonrespondents found that respon-

TABLE 1.—*Characteristics of Adult Primary Care and Obstetrics-Gynecology Clinician Respondents*

Characteristic	*Adult Primary Care Clinicians (n = 624), %*	*Obstetrics-Gynecology Clinicians (n = 157), %*
Sex		
Male	68.0	42.9
Female	32.0	57.1
Age, yr		
≤44	52.6	48.1
45–65	46.6	49.4
>65	0.8	2.6
Race or ethnicity		
White	68.6	79.0
African American	1.4	1.9
Hispanic or Latino	2.4	5.1
Asian	23.2	12.1
Other	0.8	1.9
Specialty		
Internal medicine	79.6	—
Family practice	14.0	—
General practice	2.8	—
Other adult medicine	3.6	—
Obstetrics-gynecology (physician)	—	75.2
Obstetrics-gynecology (nurse practitioner)	—	24.8

dents and nonrespondents did not differ with regards to sex, age, number of years employed by the HMO, interest in using alternative therapies, and interest in having the HMO cover alternative therapies.

Clinician interest in using alternative therapies. Two thirds of adult primary care physicians and three fourths of obstetrics/gynecology clinicians expressed at least moderate interest in the use of alternative therapies to treat health problems, alone or in combination with more conventional western medicine approaches, and 35% of adult primary care physicians and 45.3% of obstetrics-gynecology clinicians were very interested. Among the obstetrics-gynecology clinicians, nurse practitioners were more likely than physicians to be very interested in alternative therapy use (78.9% versus 35.3%; $P < .001$).

The level of interest was significantly associated with age and sex among both adult primary care physicians and obstetrics-gynecology clinicians, with women and clinicians younger than 55 years significantly more likely to be very interested in alternative therapy use than men and clinicians aged 55 and older. The level of interest was also significantly associated with clinicians' report of how often patients mentioned using or considering alternative therapies ($r = 0.35$, $P < .001$). Results of the multivariate model showed that clinicians' report of how often patients mentioned alternative therapies was a consistently significant independent predictor of clinician interest for both adult primary care physicians and obstetrics-gynecology clinicians ($P < .001$), after controlling for age group (significant predictor for adult primary care physicians) and sex (significant predictor for obstetrics-gynecology clinicians).

Among those who were at least moderately interested, nearly all indicated that this interest was motivated by problems presented by patients who could not adequately be treated with more conventional methods (60% indicated this as motivating interest "a great deal") (Figure 1). The belief that many health problems could be more effectively treated using a holistic approach in lieu of a more conventional western approach was indicated as motivating interest by nearly 85% (with about a third indicating this as motivating interest "a great deal"). A substantial proportion of clinicians also indicated that growing patient requests for these methods and the belief that the HMO must start offering these methods to remain competitive were making them more interested in alternative therapies, but most providers rated these last factors as only somewhat motivating interest.

Use of or recommendation of alternative therapies by physicians. Overall, 93% of both adult primary care physicians and obstetrics-gynecology clinicians had used or recommended to patients at least 1 of the 20 alternative therapies during the previous 12 months, or 89% if we exclude psychological counseling, 12-Step or support groups, religious healing or prayer, and special diet (which was often low fat or low sodium). The percentages of adult primary care physicians and obstetrics-gynecology clinicians who had used or recommended the use of each of the different therapies are shown in Table 2. Among adult primary care physicians, psychological counseling, relaxation techniques, 12-Step or support programs, acupuncture, massage therapy, chiropractic treatment, biofeedback, and acupressure were cited by at least 30%. Less than 10% reported using or recommending herbal or homeopathic medicines or megadoses of vitamins or supplements. Among obstetrics-gynecology clinicians, psychological counseling, relaxation techniques, 12-Step or support programs, meditation or mindfulness, massage therapy, acupuncture, chiropractic, and acupressure were cited by at least 30% of respondents. Obstetrics-gynecology clinicians were significantly more likely than adult primary care physicians to report recommending herbal and homeopathic medicines and megadoses of vitamins or supplements.

Chiropractic, acupuncture, acupressure, and massage therapy were primarily recommended for the management of musculoskeletal and nerve or joint pain, and biofeedback was recommended for the management of headaches. Relaxation techniques and meditation or mindfulness were primarily recommended for stress management and pain control. Hypnosis was mostly recommended for smoking cessation and pain control. Among adult primary care physicians, herbal medicines were most often recommended for treating upper respiratory tract infections, sleep problems, and fatigue, but among obstetrics-gynecology clinicians, they were mostly used for treating symptoms of menopause and PMS.

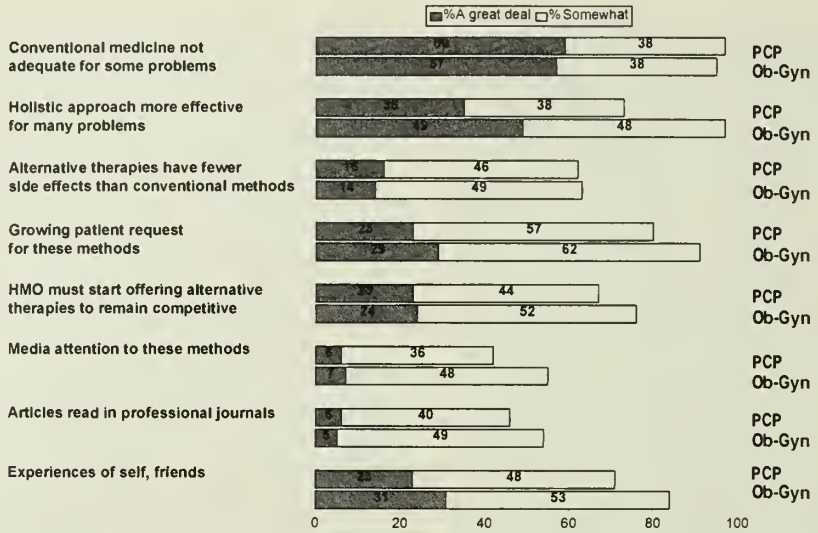


Figure 1.—These factors motivate adult primary care physician (PCP) and obstetrics-gynecology (Ob-Gyn) clinician interest in the use of alternative therapies. HMO = health maintenance organization

TABLE 2.—*Alternative Therapies Currently Being Used or Recommended by Adult Primary Care and Obstetrics-Gynecology Clinicians for Patient Care*

Alternative Therapy	*Adult Primary Care Clinicians (n = 624), %*	*Obstetrics-Gynecolagy Clinicians (n = 157), %*
Manipulation therapies	72.9	68.1
Chiropractic	33.6	37.6
Osteopathy	5.1	5.7
Acupuncture	57.2	42.7
Acupressure	30.9	30.6
Massage therapy	42.5	44.6
Body work	7.5	12.1
Ingested therapies*	29.5	54.1
Herbal or botanical medicine	8.8	29.3
Homeopathic medicine	2.7	9.5
Special diet	18.3	28.0
Megadoses of vitamins, etc	8.3	21.7
Mind-body therapies	74.8	70.7
Meditation, mindfulness	48.9	45.8
Relaxation techniques	67.6	63.7
Guided imagery, visualization	16.7	22.9
Biofeedback	31.9	22.9
Hypnosis, self-hypnosis	11.5	14.0
Movement therapies	27.7	26.1
Yoga	19.5	22.9
Tai chi, chi gong	17.9	10.2
Supportive therapies	84.9	80.2
Religious healing or prayer	13.6	12.7
12-Step program, support group	58.0	48.4
Psychological counseling	78.7	77.1

*Many of the clinicians who indicated using or recommending special diet just described the type as "low fat" or "low sodium." Thus, the prevalence reported for this modality is likely inflated by providers who recommended more conventional diets for heart disease, diabetes mellitus, and hypertension. Excluding special diet, the proportions of clinicians who reported recommending ingested therapies are 16.3% for adult primary care physicians and 42.0% for obstetrics-gynecology clinicians.

Do clinicians want alternative therapies to be covered by the HMO? Asked if they would like to see HMO health care professionals have greater opportunity to use alternative therapies to treat their patients' health problems, 65.6% of adult primary care physicians and 74.3% of obstetrics-gynecology clinicians expressed interest. About 14% of adult primary care physicians and 10% of obstetrics-gynecology clinicians said that they did not want the HMO's health care professionals to have greater access to alternative therapies for patient care, and 15% of adult primary care physicians and 9% of obstetrics-gynecology clinicians were not sure. As might be expected, interest in having expanded opportunities to use alternative therapies within the HMO was positively associated with the level of clinician interest in alternative therapies in general. Among clinicians with a high level of interest, 91.4% said that they probably or definitely wanted to have more opportunity to use these therapies with HMO patients versus 76.7% of those with moderate interest and 30.5% of those with little or no interest. The main concerns expressed about increasing access were that alternative therapies were a fad and that the therapies had not been scientifically shown to be effective.

The proportions of clinicians desiring the health plan to provide coverage for specific alternative therapies are shown in Table 3. Among both adult primary care physicians and obstetrics-gynecology clinicians, the therapies most frequently desired were acupuncture, biofeedback, acupressure, hypnosis or self-hypnosis, chiropractic, yoga, and therapeutic massage. Most adult primary care physicians indicated that they did not want herbal medicines and homeopathic medicines available. A significantly larger proportion of obstetrics-gynecology clinicians than adult primary care physicians were interested in making herbal and homeopathic medicines and massage therapy available.

TABLE 3.—*Alternative Therapies That Adult Primary Care and Obstetrics-Gynecology Clinicians Would Like the HMO to Make Available to Members*

	Would Like to Have Therapy Available	
Alternative Therapy	*Adult Primary Care Clinicians (n = 624), %*	*Obstetrics-Gynecology Clinicians (n = 157), %*
Chiropractic	52.1	57.9
Acupuncture	84.0	73.0
Acupressure	62.9	62.9
Massage therapy	43.8	61.0
Herbal, botanical medicine	15.5	44.0
Homeopathic medicine	6.9	24.5
Biofeedback	79.6	75.5
Hypnosis, self-hypnosis	56.9	63.5
Yoga	48.9	52.9

HMO = health maintenance organization

TABLE 4.—*Characteristics of Respondents to the Alternative Therapies Member Survey (n = 1,516)*

Characteristic	*Before Weighting, %*	*After Weighting, %**
Age, yr		
20–44	35.5	50.4
45–65	34.8	34.5
>65	29.7	15.1
Sex		
Female	54.9	52.5
Male	45.1	47.5
Race, ethnicity		
White	70.6	68.0
African American	5.7	5.6
Hispanic, Latino	8.6	9.6
Asian	10.6	12.0
Other	4.6	4.8
Education		
<12 yr	7.6	5.9
High school graduate	19.0	16.2
Some college	39.1	41.5
College graduate	34.4	36.4

*Weighted data reflect the actual age-sex distribution of the health maintenance organization's adult membership in the region surveyed. The profile of the 17,735 respondents to the member health survey was almost identical.

Member Survey

About 50% (n = 1,507) of the randomly stratified sample of members who were sent the alternative therapies questionnaire and 53% (n = 17,735) of those sent the general member health survey questionnaire responded. The characteristics of respondents to the member alternative therapies survey are shown in Table 4. The sample is primarily white, with most having completed at least some college or technical school and about a third having completed at least a four-year college degree. The sociodemographic characteristics of the member health survey respondent sample, which was used to estimate recent and ever use of the different alternative therapies, were virtually identical to those of the other survey sample. The telephone interviews conducted with nonrespondents found that among young and middle-aged adults, nonrespondents were similar to respondents with regard to their desire to have the HMO health care professionals incorporate more alternative treatment methods into patient care and which alternative therapies they wanted to see the HMO offer as a covered benefit. Although nonrespondents aged 65 years and older were less interested in alternative therapies than those who did respond, the survey response rate for that age group was more than 70%. Thus, response bias should not be considered a major concern.

Members' use of alternative therapies. An estimated 31% of adult HMO members had used at least one of these alternative therapies during the previous 12 months or, excluding special diet and the supportive therapies, 25%. Nearly 50% of adults had ever used at least one of these alternative therapies, 43% when special diet and the supportive therapies are excluded. The estimated proportions of adult HMO members who had used the different alternative therapies are shown in Table 5. Overall, the methods most frequently indicated were chiropractic, massage therapy, relaxation techniques, and psychological counseling. Less than 10% of adult members had used herbal or homeopathic medicines. Younger and middle-aged adults were more likely than senior adults to report having used many of these therapies.

Members primarily used the manipulative therapies such as chiropractic and acupuncture for the treatment of musculoskeletal and other pain. In addition, these modalities were being used for allergies (acupuncture and acupressure), smoking cessation (acupuncture), symptoms of PMS (acupuncture, women <44 years), and stress (acupressure and massage). Herbal and homeopathic medicines were primarily being used for upper respiratory tract infections, general health maintenance, pain, allergies, mental health or depression, stress, sleep and fatigue problems, gastrointestinal problems, and among women, managing symptoms of PMS and menopause. Meditation, relaxation techniques, and guided imagery were being used primarily for stress, pain, mental health problems or depression, general health maintenance, and PMS, and hypnosis or self-hypnosis were being used primarily for pain, stress, mental health problems or depression, smoking cessation, weight management, and sleep problems. Biofeedback was used for pain, high blood pressure, and temporomandibular joint pain.

Members' interest in alternative therapies. Members' interest in the use of alternative treatment methods to treat or prevent health conditions varies by age (Figure 2). About two thirds of younger and middle-aged adults indicated that they were at least moderately interested, and more than 40% indicated a lot of interest. Slightly less than half of senior members expressed at least moderate

TABLE 5.—*Estimated Use of Selected Alternative Treatment Methods by Adult HMO Members Ever and in Past 12 Months**

Alternative Method Used	Age 20 to 64 yr			Age ≥65 yr			Age ≥20 yr		
	Female, % (n = 7018)	Male, % (n = 5352)	All, % (n = 12,370)	Female, % (n = 2647)	Male, % (n = 2718)	All, % (n = 5365)	Female, % (n = 9665)	Male, % (n = 8070)	All, % (n = 17,735)
Manipulation therapies									
Chiropractic									
Used in past year	9.6	8.3	9.0	6.7	4.6	5.8	9.1	7.8	8.5
Ever used	24.2	24.2	24.2	18.5	19.8	19.1	23.3	23.6	23.4
Osteopathy									
Used in past year	0.2	0.1	0.2	0.2	0.4	0.3	0.2	0.2	0.2
Ever used	1.0	0.6	0.8	1.7	1.7	1.7	1.1	0.8	1.0
Acupuncture									
Used in past year	2.8	1.5	2.2	1.8	1.0	1.4	2.6	1.4	2.1
Ever used	8.5	5.1	6.8	7.9	5.9	7.0	8.4	5.2	6.9
Acupressure									
Used in past year	2.0	0.9	1.5	0.8	0.4	0.6	1.8	0.9	1.4
Ever used	4.2	2.4	3.3	2.2	1.2	1.7	3.9	2.2	3.1
Massage therapy									
Used in past year	10.2	6.1	8.2	3.5	2.6	3.1	9.2	5.6	7.5
Ever used	17.6	12.5	15.1	7.5	7.0	7.3	16.0	11.7	13.9
Body work									
Used in past year	2.0	1.7	1.8	0.5	0.9	0.7	1.7	1.6	1.6
Ever used	3.5	2.8	3.2	0.9	1.5	1.2	3.1	2.6	2.9
Ingested substances, diet									
Herbal medicine, remedies									
Used in past year	5.2	2.7	4.0	1.2	1.2	1.2	4.6	2.5	3.6
Ever used	10.0	6.3	8.2	3.8	3.1	3.5	9.0	5.8	7.5
Homeopathic medicine									
Used in past year	3.3	2.0	2.7	1.0	0.5	0.8	3.0	1.7	2.4
Ever used	5.6	3.2	4.4	2.0	0.9	1.5	5.0	2.8	4.0
Megadoses of vitamins									
Used in past year	2.5	2.3	2.4	1.7	2.0	1.9	2.4	2.2	2.3
Ever used	3.5	3.2	3.4	2.5	2.7	2.6	3.4	3.1	3.2
Special diet									
Used in past year	1.2	0.8	1.0	0.5	0.5	0.5	1.1	0.8	1.0
Ever used	2.1	1.5	1.8	1.2	0.9	1.1	2.0	1.4	1.7
Mind-body therapies									
Meditation, mindfulness training									
Used in past year	5.8	3.3	4.6	1.9	1.3	1.6	5.2	3.0	4.2
Ever used	9.0	5.3	7.2	3.6	2.2	3.0	8.1	4.8	6.6
Relaxation techniques									
Used in past year	11.4	5.4	8.5	3.6	2.1	2.9	10.2	4.9	7.7
Ever used	16.9	8.7	13.0	6.4	3.1	4.9	15.3	7.9	11.8
Guided imagery, visualization									
Used in past year	4.0	1.3	2.7	1.4	0.8	1.1	3.6	1.2	2.5
Ever used	7.1	2.5	4.9	2.6	1.1	1.9	6.4	2.3	4.5
Biofeedback									
Used in past year	0.4	0.3	0.4	0.3	0.2	0.3	0.4	0.3	0.4
Ever used	2.2	1.0	1.6	0.8	0.6	0.7	2.0	0.9	1.5
Hypnosis, self-hypnosis									
Used in past year	1.8	0.5	1.2	0.6	0.5	0.5	1.6	0.5	1.1
Ever used	4.6	1.8	3.3	2.2	1.2	1.7	4.2	1.7	3.1
Movement therapies									
Yoga									
Used in past year	3.1	1.0	2.1	1.2	0.5	0.9	2.8	0.9	1.9
Ever used	5.9	2.2	4.1	2.9	1.1	2.1	5.5	2.0	3.8

Continued on next page

Continued from previous page

Table 5.—*Estimated Use of Selected Alternative Treatment Methods by Adult HMO Members Ever and in Past 12 Months**

Alternative Method Used	Age 20 to 64 yr			Age ≥65 yr			Age ≥20 yr		
	Female, % (n = 7018)	Male, % (n = 5352)	All, % (n = 12,370)	Female, % (n = 2647)	Male, % (n = 2718)	All, % (n = 5365)	Female, % (n = 9665)	Male, % (n = 8070)	All, % (n = 17,735)
Tai chi, chi gong									
Used in past year	1.4	1.1	1.3	1.9	0.7	1.3	1.5	1.0	1.3
Ever used	2.8	2.2	2.5	3.7	1.6	2.7	3.0	2.1	2.6
Supportive therapies									
Psychological counseling									
Used in past year	8.0	3.8	6.0	1.7	1.0	1.4	7.0	3.4	5.3
Ever used	15.9	8.1	12.1	4.6	2.5	3.7	14.1	7.3	10.9
Religious healing or prayer									
Used in past year	9.5	4.9	7.3	6.1	3.4	4.8	9.0	4.7	6.9
Ever used	12.9	6.8	10.0	9.2	4.9	7.2	12.2	6.5	9.5
Support group, 12-Step program									
Used in past year	3.2	2.2	2.7	1.2	0.9	1.1	2.9	2.0	2.5
Ever used	6.7	4.4	5.6	2.5	1.8	2.2	6.0	4.0	5.1

HMO = health maintenance organization

*Estimates based on data from 17,735 respondents to a 1996 member health survey, weighted to the age-sex distribution of the adult health plan membership. The ns at the top of each column reflect the actual number of respondents who provided data.

interest, and only about a fourth were very interested. Overall, the survey results suggest that about 60% of the adult membership is at least moderately interested and 40% very interested in the use of alternative therapies.

Fairly high interest in having the HMO's health care professionals incorporate alternative treatment methods to treat health conditions in the future, either alone or combined with more usual treatments, was also indicated (Figure 3). Overall, nearly 70% of adult members would probably or definitely like to see this happen. Again, interest varied with age, with younger and middle-aged adults more likely than seniors to be interested in having alternative therapies incorporated into their HMO-delivered care.

Asked to indicate which alternative therapies they would like to have the health plan provide as a covered benefit, members most frequently expressed the desire for chiropractic, followed by massage therapy, acupuncture, relaxation techniques, and acupressure (Table 6). Among all the possible alternative therapies listed, only homeopathic medicines and biofeedback were not desired by at least 20% of adult members. As might be expected based on the general level of interest in alternative methods, seniors were less likely than younger and middle-aged adults to indicate a desire for the health plan to cover any of the methods. Also, people who had

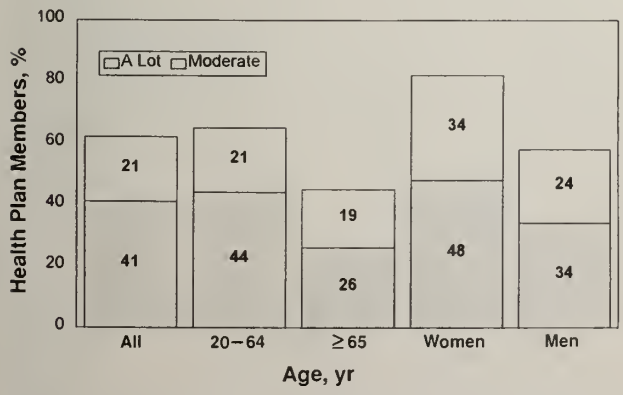


Figure 2.—The level of interest among adult health plan members in using alternative therapies to treat or prevent health problems is shown.

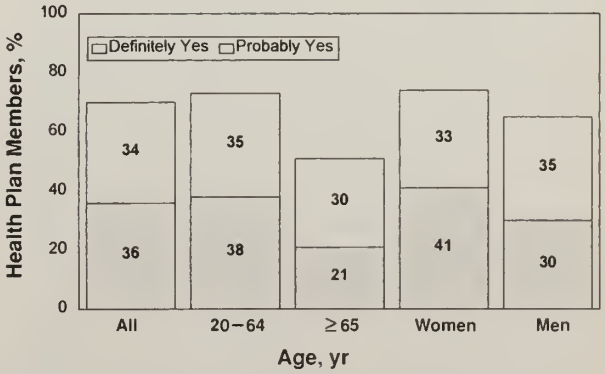


Figure 3.—The proportions of adult health plan members are shown who would like to see health maintenance organization providers use alternative methods to treat health conditions in the future.

TABLE 6.—*Alternative Therapies HMO Members Would Like to Have Covered by the Health Plan*

Alternative Therapy	All, % (n = 1516)	Age, yr 20 to 64, % (n = 1063)	>65, % (n = 453)	Sex Women, % (n = 835)	Men, % (n = 681)	Used or Considered Use of This Therapy Yes, % n†	No, % n†
Chiropractic	61.1	64.4	42.4	60.5	61.7	83.2	37.8
Acupuncture	41.4	43.8	27.5	40.0	40.0	78.2	28.1
Acupressure	33.6	36.4	17.7	36.7	30.2	76.9	22.5
Massage therapy	50.2	53.3	32.8	54.9	44.9	77.4	34.3
Herbal medicine	30.7	32.8	18.3	34.7	26.2	70.1	19.6
Homeopathic medicine	17.2	18.3	10.9	20.6	13.4	60.8	10.6
Meditation, mindfulness	23.9	26.3	10.3	26.1	21.5	62.0	13.3
Relaxation techniques	36.3	39.1	20.2	40.6	31.5	67.1	25.3
Biofeedback	17.6	18.6	11.7	20.1	14.8	49.1	14.2
Hypnosis, self-hypnosis	22.3	23.9	12.9	24.2	20.1	67.6	14.6
Yoga, tai chi	21.4	22.6	14.5	24.8	17.6	62.5	14.9

HMO = health maintenance organization

*Estimates based on data from 1,516 respondents to the member survey about alternative therapy use, weighted to the age-sex distribution of the adult health plan membership. The ns at the top of each column reflect the actual number of respondents who provided data.

†The ns on which the percentages in the last 2 columns are based are different for each therapy, and can be obtained from the lead author.

used the therapies in the past were significantly more likely than those who had not to want coverage for them in the future.

Discussion

This study found that a substantial proportion of adult members of this northern California HMO, especially young and middle-aged adults, have been using alternative therapies for their health problems, even though they usually have gone outside the health plan to do so. We also found that a substantial proportion of primary care clinicians have already been recommending alternative therapies to patients. Currently, both members and clinicians have been using alternative therapies primarily for the management of pain and problems such as PMS and menopausal symptoms. The manipulative therapies, such as chiropractic, acupuncture, and therapeutic massage, were most frequently used by both groups.

The study also found that a substantial proportion of adult primary care physicians and obstetrics-gynecology clinicians practicing in a traditional HMO are interested in incorporating alternative therapies into patient care and that most members are interested in having them do so. The primary factors motivating clinician interest in alternative therapies are their beliefs that not all problems can be effectively treated with conventional western medicines and that, at least for some problems, taking a more holistic (mind-body) approach to treatment might yield better results than using conventional treatment approaches. This is consistent with the findings of a survey of Swedish general practitioners regarding interest in alternative therapies,[27] as well as studies of why patients seek alternative treatments.[17,26,33] Although most clinicians downplayed factors of patient demand and concern that the HMO might need to offer alternative therapies to stay competitive, there was a significant association between clinicians' reports of the frequency with which patients are mentioning alternative therapy and the level of clinician interest in using these therapies.

The factors most consistently cited by clinicians as affecting whether they recommended different alternative therapies were a lack of familiarity with the methods, concern about whether they were effective, and not wanting to recommend something that their patients would need to pay for themselves. This suggests that if credible evidence were available about the effectiveness and safety of different alternative therapies for treating specific types of health problems, and if these therapies were covered by the health plan, clinicians would likely begin to recommend them more frequently, especially if demand from patients increased. Because both members and clinicians showed the greatest interest in having manipulative therapies like chiropractic, acupuncture, and massage therapy and mind-body therapies like relaxation techniques and meditation covered by the health plan, these therapies would be expected to show the greatest increase in demand if they were made more accessible through a health plan. Based on the extent of interest among primary care clinicians and members, herbal and homeopathic medicines would not be expected to be in great demand except for the treatment of certain gynecologic conditions.

The results of this study, based on the experience of one large group practice HMO in northern California, are probably not generalizable to all primary care physicians and members of HMOs around the United States. For example, the 1994 Robert Wood Johnson Foundation survey found higher usage of alternative therapies in the western United States than in other parts of the

country.[16] The geographic region served by this HMO, however, is not just the San Francisco Bay Area, which is known for leading trends in health care, but also the more conservative Central Valley of California, and the membership is diverse with regard to education, socioeconomic status, and health-related attitudes. In fact, our estimate of the proportion of members who used any of the 20 alternative therapies is comparable to that found in a 1991 national survey.[12] Patients are increasingly presenting providers with symptoms and chronic health problems that are often not totally resolved by conventional western medicines and treatments, such as stress-related disorders, pain, fatigue, PMS, and menopausal symptoms, and some patients are also expressing concern about the iatrogenic effects of the long-term use of pharmaceuticals. As more information about alternative therapies reaches people around the country suffering from these problems through media exposure, Internet searches, and disease-specific networking efforts, interest in alternative therapies among both health care professionals and the public will likely begin to mirror the current experience of this HMO. The results of this study suggest which alternative therapies are likely to be in greatest demand by these dual constituencies and should therefore be a focus for further research regarding the health conditions for which these therapies appear to be effective and ineffective and the possible costs of incorporating them into a traditional health care delivery system.

Acknowledgment

We thank Peter Lee, MD, and Lynn Bailey-Meltzer for their contributions to the conceptualization of this study and Lyn Wender and Gary Salyer for their assistance in editing and preparing the manuscript, respectively.

REFERENCES

1. Schneidman B. Response to 'The interface between complementary medicine and general practice' [Letter]. J R Soc Med 1994; 87:30

2. Abu-Realh MH, Magwood G, Narayan MC, Rupprecht C, Suraci M. The use of complementary therapies by cancer patients. Nursingconnections 1996; 9:3–12

3. Cassileth BR, Hapman BA. Alternative cancer medicine: a ten-year update. Cancer Invest 1996; 14:396–404

4. Downer SM, Cody MM, McCluskey P, Wilson PD, Arnott SJ, Lister TA, et al. Pursuit and practice of complementary therapies by cancer patients receiving conventional treatment. BMJ 1994; 309:86–89

5. Lerner IJ, Kennedy BJ. The prevalence of questionable methods of cancer treatment in the United States. Cancer 1992; 42:181–191

6. Cassileth B, Lusk E, Strouse T, Bodenheimer B. Contemporary unorthodox treatments in cancer medicine. Ann Intern Med 1984; 101:105–112

7. Clinical Oncology Group. New Zealand cancer patients and alternative medicine. N Z Med J 1987; 100:110–113

8. Cronan T, Kaplan R, Posner L, Blumberg E, Kozin F. Prevalence of the use of unconventional remedies for arthritis in a metropolitan community. Arthritis Rheum 1989; 32:1604–1607

9. Kronenfeld J, Wasner C. The use of unorthodox therapies and marginal practitioners. Soc Sci Med 1982; 16:1119–1125

10. Cleary P. Chiropractic use: a test of several hypotheses. Am J Public Health 1982; 72:727–730

11. Cherkin D, MacCornack F. Patient evaluations of low back pain care from family physicians and chiropractors. West J Med 1989; 150:351–355

12. Eisenberg DM, Kessler RC, Foster C, Norlock FE, Calkins DR, Delbanco TL. Unconventional medicine in the United States—Prevalence, costs, and patterns of use. N Engl J Med 1993; 328:246–252

13. Cohen C, Eisenberg DM, Mayer K, Delbanco TL. Prevalence of nonconventional medical treatments in HIV-infected patients: implications for primary care [Abstract]. Clin Res 1990; 38:692A

14. Smart H, Mayberry J, Atkinson M. Alternative medicine consultations and remedies in patients with the irritable bowel syndrome. Gut 1986; 27:826–828

15. Verhoef M, Sutherland L, Brkich L. Use of alternative medicine by patients attending a gastroenterology clinic. Can Med Assoc J 1990; 142:121–125

16. Paramore LC. Use of alternative therapies: estimates from the 1994 Robert Wood Johnson Foundation National Access to Care Survey. J Pain Symptom Manage 1997; 13:83–89

17. Spigelblatt L, Laine-Ammara F, Pless B, Guyver A. The use of alternative medicine in children. Pediatrics 1994; 94:811–814

18. Fisher P, Ward A. Complementary medicine in Europe. BMJ 1994; 309: 107–110

19. MacLennan AH, Wilson DH, Taylor AW. Prevalence and cost of alternative medicine in Australia. Lancet 1996; 347:569–573

20. Anderson E, Anderson P. General practitioners and complementary medicine. J R Coll Gen Pract 1988;38:511–514

21. Perkins MR, Pearcy RM, Fraser JS. A comparison of the attitudes shown by general practitioners, hospital doctors, and medical students towards alternative medicine. J R Soc Med 1994; 87:523–525

22. Swayne J. Survey of the use of homeopathic medicine in the UK health system. J R Coll Gen Pract 1989; 39:503–506

23. National Association of Health Authorities and Trusts Research. Complementary therapies in the NHS. Birmingham (Ala): National Association of Health Authorities and Trusts; 1993 (Paper 10)

24. Bouchayer F. Alternative medicines: a general approach to the French situation. In: Lewith G, Aldridge D, eds. Complementary medicine and the European community. Essex, England: CW Daniel; 1991

25. Visser JG, Peters L. Alternative medicine and general practitioners in the Netherlands: towards acceptance and integration. Fam Pract 1990; 7:227–232

26. Himmel W, Schulte M, Kochen MM. Complementary medicine: are patients' expectations being met by their general practitioners? Br J Gen Pract 1993; 43:232–235

27. Lynoe N, Svensson T. Physicians and alternative medicine—An investigation in attitudes and practice. Scand J Soc Med 1992; 20:55–60

28. Schachter L, Weingarten M, Kahan E. Attitudes of family physicians to nonconventional therapies. Arch Fam Med 1993; 2:1268–1270

29. Borkan J, Neher J, Anson O, Smoker B. Referrals for alternative therapies. J Fam Pract 1994; 39:545–550

30. Berman B, Singh B, Lao L, Singh B, Ferentz K, Hartnoll S. Physicians' attitudes toward complementary or alternative medicine: a regional survey. J Am Board Fam Pract 1995; 8:361–366

31. Cherkin D, MacCornack FA, Berg AO. Family physicians' views of chiropractors: hostile or hospitable? Am J Public Health 1989; 79:636–637

32. Moore NG. A review of reimbursement policies for alternative and complementary therapies. Altern Ther 1997; 3:26–29

33. Vincent C, Furnham A. Why do patients turn to complementary medicine? An empirical study. Br J Clin Psychol 1996; 35(pt 1):37–48

Articles

Are Critically Ill Older Patients Treated Differently Than Similarly Ill Younger Patients?

ALFRED E. STILLMAN, MD; LEONARD E. BRAITMAN, PhD; *and* RICHARD J. GRANT, MD, *Philadelphia, Pennsylvania*

Our goal was to determine whether critically ill older patients are treated differently than middle-aged patients. If so, what factors besides age contribute to that difference? Internal medicine residents (n = 46) and practicing internists (n = 41) received 8 clinical vignettes of 4 critically ill 85-year-old patients and 4 critically ill 50-year-old patients. Each patient had a distinct premorbid mental and physical state. Each respondent selected from 4 levels of therapeutic aggressiveness for each patient. The main outcome measure was the proportion of physicians who intended to treat the older of each matched pair of patients less aggressively than the younger one (that is, downgraded for age). Eight physicians (9%) treated a previously unimpaired 85-year-old patient less aggressively than a comparable 50-year-old patient. When the matched patients were either premorbidly mentally or physically impaired (but not both), about 20% of physicians downgraded for age. Most downgraded for age in matched patients who were premorbidly both mentally and physically impaired. We conclude that age alone does not engender much therapeutic bias against older patients as long as they are physically and mentally intact before the onset of their acute illness. As premorbid disabilities multiply, older patients may be treated less aggressively than younger ones with similar impairments and clinical presentations.

(Stillman AE, Braitman LE, Grant RJ. Are critically ill older patients treated differently than similarly ill younger patients? West J Med 1998; 169:162–165)

Past investigations into the attitude of medical students and physicians toward older patients have found that older patients are viewed negatively compared with younger subjects. This attitude spans respondents of both sexes and varying ages, ethnicity, and socioeconomic backgrounds. These findings have been replicated with different measuring instruments, including the Facts on Aging quiz,[1] Aging Semantic Differential Questionnaire,[2] Maxwell and Sullivan's questionnaire,[3] and John and Steel's vignettes.[4] Attitude, however, has always been difficult to measure because it can be masked by a "politically correct" answer and because older patients in these studies have usually been presented to the respondents in a generic and stereotypic manner. The objective is to measure physicians' actual behavior toward older patients. Observation and medical records review perhaps best investigate behavior, but both are expensive ventures in today's medical economic climate. Instead, we chose to examine physicians' responses to specially designed clinical vignettes.

Our study has attempted to isolate factors in addition to age that influence physicians' therapeutic behavior toward older patients. We questioned physicians about their intended therapeutic decisions for critically ill older patients with distinct premorbid mental and physical states and compared these with their intended therapeutic decisions for critically ill middle-aged persons with similar premorbid mental and physical states.

Patients and Methods

We controlled for patients' acute illness severity, age, and premorbid mental and physical capacity. A set of eight vignettes was constructed in which three variables (age, premorbid mental capacity, and premorbid physical capacity) were presented (Figure 1). The vignettes compared a 50-year-old and an 85-year-old man with similarly severe medical illnesses whose prognostic similarity had been verified by a panel of chief medical residents and other experienced clinicians. The order of presentation of the vignettes was scrambled to divert the respondents' attention from the real purpose of the questionnaire—to record their intended behavior toward ill older patients. Each

From the Division of Geriatrics and the Office for Research and Technology Development, Albert Einstein Medical Center (Drs Stillman, Braitman, and Grant), and the Department of Medicine, Temple University Medical School (Dr Grant), Philadelphia, PA. When this article was written, Dr Stillman was a fellow in geriatrics at Albert Einstein Medical Center. He is now in private practice in geriatrics.

Preliminary results of this article were presented at the Gerontological Society of America meeting in Washington, DC, November 1996.

Reprint requests to Alfred E. Stillman, MD, Home Visit Doctors, Two Penn Blvd, Ste 115, Philadelphia, PA 19144.

ABBREVIATIONS USED IN TEXT

CI = confidence interval
DNR = do-not-resuscitate

respondent was asked to choose one of four levels of therapeutic aggressiveness for patients described in each of the eight vignettes (Figure 1). Another section of the questionnaire obtained basic demographic data (age, sex, location of medical school, and year of graduation).

The questionnaires were given to two groups of respondents: internal medicine residents (PGY1-4) attending an American College of Physicians Associates conference in Pennsylvania (n = 46) and older seasoned clinicians attending another state American College of Physicians meeting (n = 41). These respondents were assured of the anonymity of their responses. The questionnaires presented to each group were identical except for the requested demographic data and vignette 3. After the test had been administered to the resident group, a few senior geriatricians felt that vignettes 3 and 6 were not truly comparable because the patient with Down syndrome was not as severely impaired mentally and physically as the geriatric patient with late-stage Alzheimer's disease. A new version of vignette No. 3 was included in the questionnaires given to the more senior clinicians (end of Figure 1).

Ninety-five percent confidence intervals (95% CI) of proportions were presented. Fisher's exact test compared proportions in different groups. A response was defined as downgraded for age when the respondents specified less intensive treatment for the 85-year-old patient than for the 50-year-old patient in a matched pair of vignettes. McNemar's test was used to compare the paired percentages of downgrading for age in patients with different combinations of premorbid mental and physical impairment. All *P* values are two-tailed. Analyses were performed using a commercially available statistical software (Statistical Package for the Social Sciences [SPSS] for Windows 7.5, SPSS Inc, Chicago, Ill).

Results

The study group consisted of 37 male and 9 female residents and 36 male and 5 female seasoned practitioners. Of the total group, 43 were US medical graduates and 44 were international medical graduates (from North or South America, Europe, Asia, or Africa). Ages ranged from 26 to 80 years, with a median of 38 years. The years since obtaining a medical degree ranged from 1 to 53, with a median of 10 years.

The frequency of downgrading the level of treatment in 85-year-old patients compared with 50-year-old patients was similar in residents and practicing internists ($P > .27$; data not shown). By combining the results for residents and experienced practitioners, we see that only 8 (9%) (95% CI, 4%–17%) physicians intended to treat the previously healthy older patient less aggressively than the previously healthy middle-aged patient (Table 1). When both patients had impaired mental but intact physical status prior to the acute illness, however, 16 (18%) (95% CI, 11%–28%) downgraded treatment of the 85-year-old patient compared with the 50-year-old patient. When both patients had intact mental but impaired physical states premorbidly, 18 (21%) (95% CI, 13%–31%), downgraded for age ($P = .77$). There was less age downgrading in patient pairs with no premorbid impairment than with one physical impairment ($P = .006$) or with one mental impairment ($P = .04$). When both patients had impaired premorbid mental and physical states, 53 physicians (61%) downgraded for age.

Although the premorbid states of the globally impaired 50-year-old patient presented to the residents and practitioners differed slightly (see both versions of vignette 3 in Figure 1), most of both groups (32 of the 46 residents and 21 of the 41 practitioners) would still have treated the 85-year-old patient less aggressively. Physicians downgraded the treatment level of the 85-year-old patient compared with the 50-year-old patient with both premorbid mental and physical impairments. This was much less pronounced in the matched pairs of patients with only one such impairment. This finding held for both residents and seasoned practitioners ($P < .004$ for all 4 comparisons, Table 1).

We investigated the associations between the responses to the vignettes and demographic characteristics of the respondents. The five demographic variables were resident or practitioner, age, sex, number of years since receiving medical degree, and US or international medical graduate. Downgrading treatment aggressiveness in the older patient of each premorbidly similar pair showed no correlation with any demographic variable ($P > .19$ for each variable).

Discussion

Our results indicate that age alone did not engender much therapeutic bias against critically ill older patients as long as they were physically and mentally intact before the onset of their acute illness. As disabilities multiplied, physicians chose less aggressive treatment options for critically ill 50-year-old patients, but that tendency was far more pronounced for 85-year-old patients. As premorbid disabilities multiply, older patients may be treated less aggressively than younger age groups with similar impairments and clinical presentations.

We also found no statistical differences in age downgrading over the five measured demographic characteristics. Thus, our study conclusions are applicable over a wide range of residents and seasoned practitioners of varying age, sex, length of medical experience, and country in which the medical degree was earned.

The anonymous clinical vignette questionnaire is a useful method to investigate the influence of patient's age on physicians' therapeutic decisions and to separate patient's age from other factors. Other recent studies have used a standard of "do-not-resuscitate" (DNR)

For each of the following vignettes, please check which of the following most closely agrees with your plan of treatment:

a) Admit to ICU and use all available therapeutic and technological support without restriction.
b) Admit to floor and treat with appropriate IV medications and nasal O_2. The patient is a "Full Code."
c) Admit to floor and treat with appropriate IV medications and nasal O_2. The patient is a No Code.
d) Make patient comfortable. Do not otherwise intervene therapeutically.

Case 1

A 50-year-old man is admitted to the hospital with a history of sudden onset of crushing substernal chest pain and shortness of breath. Physical examination reveals a blood pressure of 70/50 mm of mercury and bilateral massive pulmonary edema. The patient is an avid tennis player and is a senior partner in a law firm.

__a __b __c __d

Case 2

An 85-year-old man is admitted to the hospital with a history of insulin-dependent diabetes mellitus and recent onset of fever, chills, cough, and dyspnea. His chest x-ray film reveals massive bilateral pneumonia. His blood sugar is 900 with positive serum acetone. Arterial blood gas values: pH 7.10, pO_2 45, pCO_2 80. Serum electrolytes: sodium 125, potassium 6.5, chloride 90, CO_2 10. Until today, the patient was able to accomplish all basic activities of daily living (walking, eating, bathing, toileting, and dressing) without assistance but has become progressively forgetful over the past 3 years.

__a __b __c __d

Case 3

A 50-year-old man is admitted to the hospital with a history of sudden onset of crushing substernal chest pain and shortness of breath. Physical examination reveals a blood pressure of 70/50 mm of mercury and bilateral massive pulmonary edema. The patient has Down syndrome. He suffered burns of both hands on a stove at age 20. Despite multiple attempts at plastic surgical repair, his hands remain nonfunctional. He lives in a shelter.

__a __b __c __d

Case 4

An 85-year-old man is admitted to the hospital with a history of insulin-dependent diabetes mellitus and recent onset of fever, chills, cough, and dyspnea. His chest x-ray reveals massive bilateral pneumonia. His blood sugar is 900 with positive serum acetone. Arterial blood gas values: pH 7.10, pO_2 45, pCO_2 80. Serum electrolytes: sodium 125, potassium 6.5, chloride 90, CO_2 10. The patient walks 2 miles per day and runs a real estate business.

__a __b __c __d

Case 5

A 50-year-old man is admitted to the hospital with a history of sudden onset of crushing substernal chest pain and shortness of breath. Physical examination reveals a blood pressure of 70/50 mm of mercury and bilateral massive pulmonary edema. The patient was wounded in Vietnam and required bilateral above-the-knee amputations. He is married and works as an actuary.

__a __b __c __d

Case 6

An 85-year-old man is admitted to the hospital with a history of insulin-dependent diabetes mellitus and recent onset of fever, chills, cough, and dyspnea. His chest x-ray reveals massive bilateral pneumonia. His blood sugar is 900 with positive serum acetone. Arterial blood gas values: pH 7.10, pO_2 45, pCO_2 80. Serum electrolytes: sodium 125, potassium 6.5, chloride 90, CO_2 10. He developed Alzheimer's-type dementia 10 years ago and now resides in a nursing home where he has stage III pressure ulcers and contractures of all his extremities.

__a __b __c __d

Case 7

A 50-year-old man is admitted to the hospital with a history of the sudden onset of crushing substernal chest pain and shortness of breath. Physical examination reveals a blood pressure of 70/50 mm of mercury and bilateral massive pulmonary edema. He lives with his wife and tends a large garden. He has taken neuroleptic agents for psychotic agitation and auditory hallucinations for years. Drug side effects have required a decrease in dosage with correspondingly increasingly severe psychotic behavior.

__a __b __c __d

Case 8

An 85-year-old man is admitted to the hospital with a history of insulin-dependent diabetes mellitus and recent onset of fever, chills, cough, and dyspnea. His chest x-ray reveals massive bilateral pneumonia. His blood sugar is 900 with positive serum acetone. Arterial blood gas values: pH 7.10, pO_2 45, pCO_2 80. Serum electrolytes: sodium 125, potassium 6.5, chloride 90, CO_2 10. He suffered a right CVA with left hemiparesis 5 years ago and ambulates with a walker. He and his wife lead an active social life at their senior citizens' condominium.

__a __b __c __d

Vignette 3 Presented to the Practitioner Group

Case 3

A 50-year-old man is admitted to the hospital with a history of sudden onset of crushing substernal chest pain and shortness of breath. Physical examination reveals a blood pressure of 70/50 mm of mercury and bilateral massive pulmonary edema. The patient has Down syndrome; he is severely mentally incompetent and has been uncommunicative since birth. He suffered burns of both hands on a stove at age 20. Despite multiple attempts at plastic surgical repair, his hands remain nonfunctional. He has been institutionalized since birth.

__a __b __c __d

Figure 1.—These vignettes were presented to house officer and practitioner groups (with the exception of vignette 3, which was changed for the practitioner group [see end of figure]). CVA = cerebrovascular accident, ICU = intensive care unit, IV = intravenous, O_2 = oxygen

orders to determine physicians' possible therapeutic bias against older patients. Wenger and co-workers found that older patients were more likely to receive DNR status even after adjustment for their prognosis and functional (cognitive, ambulatory, and continence) states and that this increased directly with advancing age past 65 years.[5] Hakim and associates found that "DNR orders were written most rapidly for persons older than a threshold of 75 years of age."[6 p 291] However, DNR orders reflect many factors pertaining to the patient, the patient's family, and

TABLE 1.—*Fraction of Respondents (n = 87) Who Downgraded Treatment of the Older Patient Compared With the Middle-aged Patient**

	Mentally Intact	*Mentally Impaired*
Physically intact	8/87	16/87
Physically impaired	18/87	53/87†

*See "Results" section for paired comparisons of age downgrading in above 4 categories.
†Thirty-two of 46 residents and 21 of 41 practitioners.

the physician, including the physician's previous life experiences, medical training, and the specific socioeconomic environment in which the physician works.[6,7] It is difficult, if not impossible, to separate these factors and analyze their effect on DNR orders. Such studies have been conducted by either or both medical records review and patient, family, and physician interview. Either of these methods breaches physician anonymity, a problem not encountered with our anonymous and confidential questionnaire. Also, medical records review or personal interview studies are complicated by physicians' need to deal with many different diseases, each of whose presentation or course in their patients may be highly variable. On the other hand, the vignette represents a more focused assessment of physicians' treatment predispositions because responses are triggered by specific information related only to three variables of interest (age, premorbid mental state, and premorbid physical state). The specific information presented to respondents individualizes each patient. All respondents reviewed the same vignettes; only two diseases (which had been screened by a physician panel for prognostic similarity) with identical clinical presentations were used. The clinical vignette, when used appropriately, can help clarify thought processes leading to medical decisions.

These results stimulate further questions. What factors other than premorbid mental and physical states (such as degree of patient's or family's interest, patient's financial status, or degree of patient's dependency in living arrangements) might influence physicians' behavior toward a critically ill older patient? How are these results influenced by a physician's method of remuneration? Ethically, why should a premorbidly globally impaired and severely ill young person be regarded or treated differently than a similar older patient? How would older persons themselves respond to these same vignettes when they have been "translated" into lay language? The last question is under investigation by our group.

REFERENCES

1. Palmore E. Facts on Aging: a short quiz. Gerontologist 1977; 17:315–320

2. Rosencranz HA, McNevin TE. A factor analysis of attitudes toward the aging. Gerontologist 1969; 9:55–59

3. Maxwell AJ, Sullivan N. Attitudes toward the geriatric patient among family practice residents. J Am Geriatr Soc 1980; 28:341–345

4. John A, Steel K. Interest in geriatrics at a university department of medicine. J Am Geriatr Soc 1978; 26:149–156

5. Wenger NS, Pearson ML, Desmond KA, Brook RH, Kahn KL. Epidemiology of do-not-resuscitate orders: disparity by age, diagnosis, gender, race, and functional impairment. Arch Intern Med 1995; 155:2056–2062

6. Hakim RB, Teno JM, Harrell FE Jr, Knaus WA, Wenger N, Phillips RS, et al. Factors associated with do-not-resuscitate orders: patients' preferences, prognoses, and physicians' judgments. SUPPORT Investigators—Study to Understand Prognoses and preferences for Outcomes and Risks of Treatment. Ann Intern Med 1996; 125:284–293

7. Hanson LC, Danis M, Garrett JM, Mutran E. Who decides? Physicians' willingness to use life-sustaining treatment. Arch Intern Med 1996; 156:785–789

Epitomes

Important Advances in Urology

Urology

Daniel A. Nachtsheim, MD, Section Editor

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in urology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, as to both scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in urology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Urology of the California Medical Association, and the summaries were prepared under the direction of Dr Nachtsheim and the Panel.

Informing Patients About the PSA Test: A New Requirement

A NEW LAW in California requires a physician who examines a patient's prostate gland to inform that patient of the prostate specific antigen (PSA) test if the patient falls into one of four broad categories. The 1997 law was created by Senate Bill 1, carried by California's Senate President Pro Tempore and written on behalf of a popular lobbyist who was seriously ill with prostate cancer (full text of SB1 follows on page 167). Along with many other professional groups, California's medical association has clear policy opposing statutory requirements for physicians that prejudice the exercise of their clinical judgment. In the circumstances of SB 1, The Medical Association worked with the author so that the final version of the bill no longer carried criminal penalties for non-complying physicians and used Patient Section Criteria based on American Urological Association recommendations.

The enacted bill requires a physician to provide information on "the availability of appropriate diagnostic procedures, including but not limited to, the prostate specific antigen (PSA) test" if the physician for any reason examines the patient's prostate gland and *any* of the following applies: the physician believes it is medically necessary to provide the required information, *or* the patient is over 50 years of age, *or* manifests clinical symptomatology, *or* is at increased risk of prostate cancer.

Enactment of SB 1 should not create major changes in the practice of many California physicians who conduct a rectal exam for the purpose of detecting prostate cancer (as opposed to other possible reasons) and are already accustomed to discussing the potential risks and benefits of prostate specific antigen tests (PSA) and other diagnostic procedures for prostate cancer. This discussion usually includes reference to the current range of scientific statements on the appropriate use of PSA screening and facts most relevant for patient decision making. For example, the American Urological Association (AUA), which has revised its recommendations since SB1 became law, now endorses the American Cancer Society (ACS) recommendations. Their joint policy suggests offering a PSA test and digital rectal examination to men in approximately the same categories as outlined by SB 1, and also includes the statement that "Screening for prostate cancer in asymptomatic men can detect tumors at a more favorable stage (anatomic extent of the disease). There has been a reduction in mortality from prostate cancer, but it has not been established that this is a direct result of screening." The National Cancer Institute finds insufficient evidence to recommend serum tumor markers such as the prostate specific antigen test, while the American College of Physicians (ACP) recommends an individualized decision of whether to screen a patient with a digital rectal exam or prostate specific antigen test. The ACP also suggests statements that could be given to the patient in making this decision. These include information on false-positive and false-negative results, the current lack of proof of the benefits of screening and aggressive treatment of prostate cancer, and the relatively high probability that further invasive evaluation will be required as a result of testing.

Some physicians laud SB 1's intent to increase discussion between physicians and patients of prostate cancer detection, but note that the law's requirements are too broad. A digital rectal exam that includes palpation of the prostate may be conducted on any patient to detect occult bleeding, to determine prostate position, or for other reasons unrelated to suspicion of prostate cancer. Physicians who ignore the prostate specific antigen test and other patient information requirements of SB 1 can be prosecuted by the Medical Board for unprofessional conduct. In a larger context, SB 1 is an example of elected officials

Bill Number: SB 1 Chaptered
Chapter 11

Filed with Secretary of State May 20, 1997
Introduced by Senator Burton

December 2, 1996

An act to add Section 2248 to the Business and Professions Code, relating to health, and declaring the urgency thereof, to take effect immediately.

The People of the State of California do enact as follows:
Section 1. Section 2248 is added to the Business and Professions Code, to read:
2248. This section shall be known as, and may be cited as, the Grant H. Kenyon Prostate Cancer Detection Act.

(a) If a physician and surgeon, during a physical examination, examines a patient's prostate gland, the physician and surgeon shall provide information to the patient about the availability of appropriate diagnostic procedures, including, but not limited to, the prostate antigen (PSA) test, if any of the following conditions are present:

(1) The patient is over 50 years of age.

(2) The patient manifests clinical symptomatology.

(3) The patient is at an increased risk of prostate cancer.

(4) The provision of the information to the patient is medically necessary, in the opinion of the physician and surgeon.

(b) Violation of subdivision (a) constitutes unprofessional conduct and is not subject to Section 2314.

Section 2. This act is an urgency statute necessary for the immediate preservation of the public peace, health, or safety within the meaning of Article IV of the Constitution and shall go into immediate effect. The facts constituting the necessity are:
Prostate cancer is currently a leading cause of cancer death in males in this country. In order to save as many people's lives from this deadly disease as soon as possible through public awareness of the availability of early detection procedures, it is necessary that this act take effect immediately.

responding to important medical issues by incorporating elements of clinical practice guidelines in effect at that time into legal requirements. It is important for physicians to understand these legal requirements while they seek to apply an evolving body of knowledge to the individual patient in their care.

PHILLIP WISE, MD
San Diego, California

KATHRYN DUKE, MPH, JD
San Francisco, California

REFERENCES

American Urological Association, Inc®. Early Detection of Prostate Cancer. Board of Directors, September 1997 (revised)

American Cancer Society. Cancer Facts & Figures 1998: Special Section: Prostate Cancer. 1998. Available: http://www.cancer.org/statistics/cff98/special.html. 8/10/98

National Cancer Insitute. PDQ® Detection & Prevention—Health Professionals. 1998. Available: http://cancernet.nci.nih.gov/clinpdq/screening/Screening_for_prostate_cancer_Physician.html#1. 8/10/98

American College of Physicians guidelines. Ann Intern Med 1997; 126(6): 468–479

The Urethral Sling and Stress Urinary Incontinence

STRESS URINARY INCONTINENCE affects between 15–60% of women, and has a tremendous impact on a woman's quality of life. Incontinence is either urgency or stress in nature. Urgency incontinence and mild SUI can be successfully managed in general with behavioral or anticholinergic treatment. Moderate to severe SUI is best managed by operative intervention. The following epitome discusses the role of urethral slings in the management of SUI.

Stress urinary incontinence is defined as the involuntary loss of urine related to increases in abdominal pressure resulting from activities such as laughing, coughing, lifting, and positional changes. Two factors are important to the development of stress urinary incontinence: urethral hypermobility and/or intrinsic sphincteric deficiency. Both factors commonly coexist and vary in their relative contribution in women with stress urinary incontinence. Hypermobility is the rotational descent of the proximal urethra and bladder neck into the vagina when there are increases in intra-abdominal pressure. Intrinsic sphincteric deficiency refers to a deficiency in urethral sphincter function, and is generally unrelated to urethral support. All operative procedures for stress urinary incontinence address either or both of these factors. The selection of a surgical procedure for stress urinary incontinence therefore depends on the relative contributions of urethral hypermobility and intrinsic sphincteric deficiency. Stress urinary incontinence related primarily to bladder neck hypermobility can commonly be corrected with routine bladder neck suspensions or urethral slings. If, however, urethral sphincteric deficiency is the primary cause of stress urinary incontinence, urethral bulking agents, artificial urinary sphincters, and sling procedures are appropriate. Of the treatment modalities mentioned, the urethral sling is the only procedure that addresses both the hypermobile urethra and intrinsic sphincteric deficiency. In addition, there has been a relatively recent realization that intrinsic sphincteric deficiency plays a more prominent role in stress urinary incontinence than previously believed. These two factors have led to an increase in the popularity of the urethral sling procedure.

In 1910, Goebell introduced the concept of a urethral sling by using reflected pyramidalis muscle as a bolster for the urethra. This is analogous to a leather seat supporting a child on a swing. Since then, several modifications using different autologous (e.g. rectus fascia, fascia lata, vaginal wall) as well as synthetic (e.g. mersilene, Gortex, Marlex) materials have been used. The utility of synthetic materials, however, is limited because of complications including bladder erosion, infection, and fistula formation. There has been a recent interest in the use of homologous tissue for urethral slings, and the initial results appear promising.

Approaches to the urethral sling can be classified as transabdominal, transvaginal, and a combination of both. There is no compelling evidence that one approach is

superior to the others. The type of operation is best determined by surgeon preference and experience. Regardless of approach, the principles are the same: a broad base support directly under the urethra, which is placed with only minimal tension.

The American Urologic Association Female Stress Urinary Incontinence Clinical Guidelines Panel conducted a comprehensive review and in-depth analysis of published outcome data pertaining to different surgical procedures for urinary incontinence. This panel concluded that urethral slings, along with retropubic bladder neck suspensions, are the most efficacious procedures for long-term success in the treatment of urinary incontinence secondary to urethral hypermobility. They report a greater than 85% probability of improvement of urinary incontinence at 48 months or longer with the use of urethral slings. Although outcome literature is sparse for patients with intrinsic sphincteric deficiency treated with slings, it was the panel's opinion that this procedure is also an effective type of treatment for intrinsic sphincteric deficiency patients. Possible complications of sling procedures include prolonged urinary retention, urgency and urgency-related incontinence. The risk of postoperative urgency ranges from 7–46% and can be quite debilitating to the patient. Urinary urgency is best managed with behavioral training (fluid moderation, timed voiding, pelvic floor exercises) or anticholinergic medications. In general, if urgency is present preoperatively, there is a significant risk that these symptoms will persist postoperatively. The risk of permanent retention, however, is low at less than 5% and can be managed with clean intermittent catheterization or urethrolysis.

The urethral sling addresses urethral hypermobility and may address intrinsic sphincteric deficiency. This versatility, along with excellent cure rates and low complication rates, have led many to apply this operation to most types of stress urinary incontinence to those patients who have opted for surgical intervention.

H. Roger Hadley, MD
Elmer B Pineda, MD
Lama Linda, Califarnia

REFERENCES

Leach GE, Dmochowski RR, Appell RA, Blaivas JG, Hadley HR, Luber KM, Mostwin JL, O'Donnell PD, Roehrborn CG. Female Stress Urinary Incontinence Clinical Guidelines Panel summary report on surgical management of female stress urinary incontinence. J Urol 1997; 158:875–880

Baldwin DD, Hadley HR. Stress urinary incontinence. In: Urinary incontinence. p. 190-197. O'Donnell PD, editor. Mosby-Year Book, Inc; 1997. St. Louis, Missouri

Peyronie's Disease: A Difficult Sexual Dysfunction Problem

Peyronie's disease is a physically and psychologically devastating problem that affects up to 2% of men. Those affected are primarily between the ages of forty and sixty. Peyronie's disease is manifested by fibrous, inelastic scar tissue involving the tunica albuginea of the penis, the fibrous jacket surrounding the spongy, vascular tissue of the corpora cavernosa, which expands during the development of an erection. The inelastic scar is palpable in the flaccid penis, but a penile deformity such as bending, narrowing, hinging, and/or shortening can be visible when the penis becomes erect. Painful erections may occur particularly in the early phase of the disease. All of these changes can result in difficulty with vaginal penetration and may be further exacerbated by concomitant disorders such as diabetes, hypertension, elevated serum lipids, or a smoking history that could cause decreased arterial inflow or venous leakage.

The disease received its name in the 1740s from Francois de la Peyronie, who was the first surgeon to King Louis XV. Despite all treatment options available since then, it still remains a therapeutic dilemma. Most commonly, the characteristic Peyronie's plaque is found on the dorsum of the penis causing an upward curvature during erection. However, other plaque locations can occur, resulting in various penile deformities. To understand how the erection deformity occurs, imagine the effect of placing a piece of tape on a child's balloon. As the balloon expands, it will curve around the inelastic segment caused by the tape.

The cause of Peyronie's disease remains an enigma. There have been many theories, including sexually transmitted, inflammatory, or autoimmune. The mechanical injury theory suggests that trauma to the erect penis activates the disease process. More current proposals suggest that Peyronie's disease may, in fact, be a wound healing disorder, much like a keloid or hypertrophic scar. It has been noted in patients with Peyronie's disease that elastin, the protein which allows for normal tunical expansion, is decreased or abnormal in the outer jacket. Therefore, pressure on the erect penis during intercourse can stretch the tunical fibers, and, due to the decreased tolerance to stress, a delamination or fracture injury typically involving the septal and inner circular fibers of the tunica may occur. Following injury, the release of cytokines activate fibroblast proliferation and collagen, the primary extracellular matrix component of a Peyronie's plaque, is produced. Disregulation in the genetic code could cause a loss of balance between scar formation and remodeling. The result is the deposition of an exuberant scar which does not remodel properly.

Although Peyronie's disease may resolve spontaneously, this appears to be uncommon (around 15%). Treatment options include conservative therapy, which is the treatment of choice for many patients (30%). This would include observation of the man who has minor curvature (e.g. <30°), which does not interfere with his ability to have sexual relations, and neither he nor his partner experience pain during intercourse. This patient should be reassured that this is a disease that will not degenerate into malignancy. Oral therapies have also been used, although there is no clear, reliable, efficient choice. The most common oral medications currently used are vitamin E, Potaba (potassium aminobenzoate) and colchicine. Drugs injected directly into the plaque have also been used, including steroids, verapamil, and collagenase. The use of steroids has fallen out

of favor due to significant failure rates and uncommon but worrisome side effects, including local tissue atrophy and adrenal suppression. Verapamil, a calcium channel blocker known to change fibroblast function in vitro in doses that can be achieved by intralesional administration, has been used clinically with reported success.

Fibroblasts exposed to calcium channel blockers change from stimulating a synthetic cell manufacturing scar to more of a degradative process. Clinical trials with intralesional verapamil injections into a Peyronie's plaque show positive effects in about 60% of patients with respect to deformity improvement and in 75% by subjective report. Over 70% of patients have improved sexual function. For those patients with acute disease associated with painful erections, 97% have rapid resolution of their penile pain with 1 to 4 injections. Typically, 10 mg of this drug diluted up to 10 ccs with saline is injected into the Peyronie's plaque after performing a buprivical penile block to anesthetize the penis (6–12 sessions). No cardiovascular or hypotensive events have been noted. The primary side effect is ecchymosis due to the puncturing of the subcutaneous tissues, 2-3 punctures in the skin and 200-300 in the plaque. It appears that modifiers of cytokine and fibroblast function may be the future for therapy of early Peyronie's disease.

Surgery is used for patients with more advanced deformity and/or decreased rigidity. Tunica plication is a type of surgery that straightens the penis by shortening the long side (convex) of the penis to equal the shorter side. Plaque incision or excision has also been employed successfully. The defect created in the tunica is patched with a variety of autogolous tissues, including dermis, vein and temporalis fascia. In the man who has penile deformity as well as insufficient rigidity, then placement of a penile prosthesis is indicated.

In conclusion, therapeutic advances have not resulted in a reliable cure to this problem, probably because of an incomplete understanding of the basic pathophysiology of Peyronie's disease. Recent advances in the understanding of wound healing and its disregulation may offer new treatment options such as modifiers of cytokine and fibroblast function. Eventually, multimodality protocols may be developed that might include combined collagenase/verapamil intralesional injections with concurrent oral therapy, such as colchicine, to stabilize or improve the deformity. Of course, for those patients who do not succeed with conservative therapy, surgery may be offered. Surgery is also indicated for patients with severe deformity, extensive plaque calcification, those who have failed conservative therapy or have erectile failure, or any patient who insists upon a more rapid, reliable result.

Laurence A. Levine, MD
Chicago, Illinois

REFERENCES

Devine CJ Jr. Proposal: Trauma as the cause of the Peyronie's lesions. J Urol 1997; 157:285–290

Levine LA. Treatment of Peyronie's disease with intralesional verapamil injection. J Urol 1997; 158:1395–1399

Weidner W. Sexual dysfunction in Peyronie's disease: an analysis of 222 patients without previous local plaque therapy. J of Urol 1997; 157:325–328

ADVISORY PANEL TO THE SECTION ON UROLOGY

RAYMOND FAY, MD
Advisory Panel Chair
CMA Council on Scientific Affairs Representative
San Francisco

DANIEL A. NACHTSHEIM, MD
CMA Section Chair
La Jolla

HARRY NEUWIRTH, MD
CMA Section Assistant Secretary
Greenbrae

HERBERT RUCKLE, MD
Loma Linda University

HARCHARAN S. GILL, MD
Stanford University

RALPH W. DEVERE WHITE, MD
University of California, Davis

THOMAS E. AHLERING, MD
University of California, Irvine

RICHARD M. EHRLICH, MD
University of California, Los Angeles

JOSEPH D. SCHMIDT, MD
University of California, San Diego

PETER R. CARROLL, MD
University of California, San Francisco

STUART BOYD, MD
University of Southern California

HARRY NEUWIRTH, MD
Northern California Urological Society
Greenbrae

PHILLIP WISE, MD
San Diego Urological Society
La Jolla

DAVID W. RHODES, MD
Los Angeles Urological Society
Pasadena

ASHOK J. KAR, MD
Orange County Urological Society
Santa Ana

KATHY A. DESANTIS
Invited Guest
Santa Ana

KATHRYN DUKE, JD, MPH
CMA Staff
San Francisco

LESLIE BIRNBAUM
CMA Staff
San Francisco

Alerts, Notices, and Case Reports

Unusual Vaginal Laceration Due to a High-Pressure Water Jet

JOSEPH P. RAMOS, MD
DALE CARRISON, DO, FACEP
DAVID L. PHILLIPS, MD
Las Vegas, Nevada

WITH THE GROWING popularity of water sports, the number of water-related injuries, not surprisingly, continues to increase annually. In 1994, 6,906 injuries were reported to the US Coast Guard.[1] The increased number of personal watercraft on lakes, a lack of experience and proper training, inadequate personal protective devices, and alcohol use are just a few of the factors responsible for the increasing number of injuries.[1] Lake Mead National Recreation Area, near Las Vegas, Nevada, is the National Parks Services most-visited park and the leading area for water-related injuries (Glenn Anderson, EMS Director, National Parks Services, Lake Mead; personal communication, January 1996). We report a unique case of an injury involving a personal watercraft at Lake Mead.

Although vaginal injuries related to the "water-ski douche" have been reported by many,[2–7] only three cases of vaginal injury due to the "Jet Ski douche" have been previously reported.[8–10] We introduce the first case that can be attributed to the force of the water jet alone. It involved a vaginal laceration without perforation into the abdominal cavity.

Report of a Case

The patient, a 31-year-old woman, gravida 1, para 1, was seated behind her husband on a Jet-Ski as it was launched from the shallow waters near the edge of Lake Mead. Before any forward velocity could be attained, she fell backward into the water with legs abducted and was struck directly in the perineal area by the thrust of the water jet. She was wearing a two-piece bathing suit and had been drinking alcoholic beverages before the accident. Profuse vaginal bleeding was noted immediately, and the patient lost consciousness. She was taken back to shore but for unknown reasons, 90 minutes elapsed before the patient received any emergency care in the field. When emergency medical personnel arrived, the patient was conscious, her pulse was rapid and weak, and her blood pressure was difficult to obtain. During the initial management, which included the placement of perineal packs and military antishock trousers, the patient lost and regained consciousness four times. After being stabilized, the patient was airlifted to the Las Vegas University Medical Center Trauma Department for definitive treatment. During the air transport, the patient was hypotensive with a blood pressure of 74/44 mm of mercury but responded well to a fluid challenge of 1,500 ml of a normal saline solution.

In the trauma resuscitation area, the patient was found to have a blood pressure of 106/56 mm of mercury, a pulse rate of 131 beats per minute, and a respiratory rate of 29 per minute. She had primarily perianal and vulvar pain and vomited once while in the resuscitation area. The findings of a physical examination were surprisingly unremarkable, showing only pale conjunctivae and a large blood clot in the vaginal pubic hair. No obvious external laceration or bruises were present, and abdominal pain was minimal with no rebound or guarding on examination. A vaginal examination with the use of a speculum revealed active vaginal bleeding of an undetermined location. Laboratory studies revealed a hemoglobin level of 90 grams per liter (9.0 grams per dl), a hematocrit of 0.27 (27.4%), and a leukocyte count of 3.5×10^9 per liter (3,500 per μl). The results of a computed tomographic scan of the abdomen and pelvis were indeterminate because of free air in the rectum or around the uterus. At this juncture, a gynecologic consultation was obtained. It was felt that a more thorough assessment and repair could be done under anesthesia; therefore, the patient was taken to surgery by the trauma surgery team.

In the operating room, rigid sigmoidoscopy was completed, and no evidence of a colorectal injury was found. A comprehensive vaginal examination revealed a 5-cm (2-in) deep laceration that extended around the cervix on the left lateral vaginal wall from the 12-o'clock to the 6-o'clock position. No evidence of perforation into the abdominal cavity was noted. A Penrose drain was placed and the wound closed using a 0 chromic suture.

Postoperatively, the patient's hemoglobin level and hematocrit had fallen to 56 grams per liter (5.6 grams per dl) and 0.16 (16.2%), respectively, and 3 units of blood were transfused. On postoperative day 2, a fever developed and, the patient was treated with disodium cefotetan and metronidazole hydrochloride. The remainder of the hospital stay was without complications. The patient was discharged home on postoperative day 4 with a regimen of doxycycline hyclate, metronidazole, and iron. There were no adverse sequelae.

(Ramos JP, Carrison D, Phillips DL. Unusual vaginal laceration due to a high-pressure water jet. West J Med 1998; 169:171–172)

From the Department of Emergency Medicine, University Medical Center of Southern Nevada, Nevada.

Reprint requests to Dale Carrison, DO, FACEP, Director, Emergency Department University Medical Center, Las Vegas, Nevada 89102.

Discussion

Although injuries from water sports vary in severity and presentation,[2] this case represents a unique vaginal injury resulting solely from the blast of a high-pressure water jet. Two similar cases have involved a twofold mechanism of injury: falling into the water at high speeds in addition to the blast of a water jet.[8,9] Injuries in a third reported case are presumed to be due to the blast of a high-pressure water jet, but the mechanism is not elaborated.[10] In addition, this case represents a massive hemorrhage without visceral perforation and without a dramatic emergency department presentation. Important aspects to be contemplated by treating physicians include the treatment of possible infection, the possibility of sexual abuse, a careful approach to vaginal examination in the light of a sometimes subtle presentation, and the effects of alcohol on an injured patient.

Concerning infection, some authors have avoided the prophylactic use of antibiotics after similar vaginal lacerations.[3–5] Rodgers reports, however, that wounds contaminated with vaginal secretions are considered "high risk" and probably are an indication for antimicrobial agents.[11] In addition to vaginal secretions, the normal flora of lake water may include many viral, protozoal, parasitic, and bacterial pathogens. The pathogens present will vary from lake to lake based on differences in water temperature, pH, and nutrient density.[12] Some of the more common waterborne enteric pathogens include *Escherichia coli*, *Shigella* and *Campylobacter* species, *Vibrio cholerae*, *Salmonella* species, *Yersinia enterocolitica*, and *Aeromonas hydrophila*.[12] Therefore, it is recommended that treating physicians be knowledgeable of the waterborne pathogens that predominate in their respective geographic area. In this patient, it was thought that the cost of antibiotics was far outweighed by the potential for infection, abscess formation, and other perilous sequelae.

Sexual abuse is a second consideration in any patient with vaginal trauma. It has been reported that a lack of obvious external trauma—that is, no bruising or swelling—may be a clue to abuse rather than trauma.[4] Although this viewpoint is much respected, our patient's presentation was contradictory and represents a case where the physical findings were not indicative of the cause or severity of the underlying injury. A subtle presentation highlights a third aspect of this case: the findings of the speculum examination in vaginal trauma. Gray reports a case of vaginal laceration due to a water-ski douche in which "250 ml of blood gushed out of the wound" during vaginal examination.[5] Similarly, our patient represents a case where a clot was visualized in the external pubic hair (no active bleeding), and only a history of bleeding was given. On speculum examination, however, active bleeding was noted and was most likely exacerbated or at least reinitiated by the examination. Although blood loss can be aggravated by a vaginal examination, a thorough physical examination is necessary and warranted in vaginal trauma. This includes a digital examination and a cautious speculum examination to determine the full extent of the injury.

Last, alcohol use is a major concern in trauma patients. Patients with alcohol intoxication who are injured have more blood loss, more invasive monitoring, more operative procedures, more fluid replacement, and higher oxygen requirements.[13] Taking this into account when gathering a history involving vaginal or other trauma may help guide a physician's expectations and treatment.

Preventing vaginal trauma due to the high-pressure water douche involves education. Instruction on operating personal watercrafts and the possible hazards associated with their use is essential. Personal watercraft have been reported to reach speeds as high as 55 miles per hour.[9] Most are powered by a three-blade stainless-steel impeller that forces water through a jet pump. The resulting water jet ranges from 679 lb of thrust in smaller models to in excess of 862 lb of thrust in larger models (Kawasaki Motors Corporation, 900ZXi Jet Ski specifications brochure, P/N 99969-2413, 1994). This powerful water jet, if misdirected, may be fatal. Education should begin with the basics, such as safe operating techniques and the importance of protective clothing. For example, swimsuits with more than one layer of fabric, rubber wet suits,[2–4,7] and even cutoff jeans[3] may all be deterrents to a high-pressure water blast. Besides clothing, the "dead man" switch to reduce power if a driver falls off may prevent injury to the driver of a water-jet–powered device.[9] Last, women should be cautioned on the use of tampons when engaged in water sports. It has been reported that a tampon may have a "pistonlike" effect when impacting with water and create excessive stretching forces on the vagina.[14]

REFERENCES

1. US Department of Transportation, United States Coast Guard. Boating statistics 1994. Washington (DC): Government Printing Office; 1994 (Commandant Publication P16754.8)

2. Kizer KW. Medical hazards of the water skiing douche. Ann Emerg Med 1980; 9:268–269

3. Edington RF. Vaginal injuries due to water-skiing [Letter]. Can Med Assoc J 1978; 119:310–311

4. Perlman SE, Hertweck SP, Wolfe WM. Water-ski douche injury in a premenarcheal female. Pediatrics 1995; 96(pt 1):782–783

5. Gray HH. A risk of waterskiing for women [Letter]. West J Med 1982; 136:169

6. Kuntz WD. Water-ski spill and partial avulsion of the uterine cervix. N Engl J Med 1983; 309:990

7. Tweedale PG. Gynecological hazards of water-skiing. Can Med Assoc J 1973; 108:20–22

8. Wein P, Thompson DJ. Vaginal perforation due to jet ski accident. Aust N Z J Obstet Gynaecol 1990; 30:384–385

9. Haefner HK, Andersen HF, Johnson MP. Vaginal laceration following a jet ski accident. Obstet Gynecol 1991; 78:986–989

10. Muller RJ. Jet-ski injury: a case history. J La State Med Soc 1993; 145:27–28

11. Rodgers KG. The rational use of antimicrobial agents in simple wounds. Emerg Med Clin North Am 1992; 10:753–766

12. Backer HD. Field water disinfection. In: Auerbach PS, ed. Wilderness medicine. St Louis (Mo): Mosby; 1995, pp 1060–1066

13. Sommers MS, Schackmann J, Wallace M, Von Rotz N, Willhite JM. Circulatory response of young adult trauma victims with alcohol intoxication. J Subst Abuse 1994; 6:449–456

14. Niv J, Lessing JB, Hartuv J, Peyser MR. Vaginal injury resulting from sliding down a water chute. Am J Obstet Gynecol 1992; 166:930–931

Mastoiditis, Lymphoma, and AIDS

THOMAS LOWRY
LAIQ RAJA, MD
ABRAHAM VERGHESE, MD
El Paso, Texas

THE INCIDENCE OF mastoiditis has decreased in recent decades because of the availability of oral antibiotics and better treatment of acute otitis media.[1,2] In the era of the acquired immunodeficiency syndrome (AIDS), however, there has been a resurgence of conditions that before this were fairly uncommon. One group of authors has noted that the frequency of head and neck manifestations in patients with AIDS is nearly 100% during the course of their disease.[3] In addition, many authors have observed an increase in the incidence and prevalence of serous otitis media, acute otitis media, and external otitis,[1–6] but reports of mastoiditis in patients with AIDS appear less frequently.

In addition to traditional T-cell pathogens, it is now well recognized that persons infected with the human immunodeficiency virus (HIV) also have B-cell defects and problems with pathogens such as *Streptococcus pneumoniae*. Sinusitis, bacterial pneumonia, and even bronchiectasis have been described in these patients.[7]

We describe the cases of two patients with AIDS and B-cell lymphoma who presented with mastoiditis.

Report of Cases

Patient 1

The patient, a 35-year-old HIV-positive man, presented to the emergency department at Thomason Hospital, El Paso, Texas, with severe right-sided ear pain for two weeks. The patient described the pain as throbbing, with radiation to his face and jaw. He did not have blurred vision, vertigo, or drainage of fluid from his ear but did have a global headache. Two weeks before this, the patient was diagnosed with acute otitis media and was treated with a course of amoxicillin and clavulanate potassium, 500 mg three times a day, but his symptoms have only worsened since then. He had been diagnosed with HIV ten years previously, and his most recent $CD4^+$ cell count was 152×10^6 per liter (152 cells per µl). His medical history was notable for non-Hodgkin's B-cell lymphoma, *Mycobacterium avium-intracellulare*, genital herpes, anal condylomata, and a persistent perirectal fistula. Medications at admission included zidovudine, acyclovir, and the combination of trimethoprim and sulfamethoxazole.

On physical examination, the patient's temperature was 36.9°C (98.4°F), his blood pressure was 132/96 mm of mercury, his pulse rate was 94 beats per minute, and respirations were 20 per minute. An injected tympanic membrane was noted with no discernible air-fluid level or perforation. Tenderness was elicited on palpation of the right mastoid and preauricular areas, and a mild cervical lymphadenopathy was present. The findings of the physical examination were otherwise unremarkable. The leukocyte count was 4.18×10^9 per liter (4,180 per µl) (0.29 [29%] segmented neutrophils, 0.01 [1%] band forms, 0.55 [55%] lymphocytes, 0.09 [9%] monocytes, and 0.01 [1%] eosinophils). The results of serum chemistry studies were remarkable only for an elevated alkaline phosphatase level of 115 U per liter and a lactate dehydrogenase level of 241 U per liter. No specimens were taken for culture, and tympanocentesis was not performed, but computed tomography of the head showed asymmetry and increased bony densities of the right mastoid, consistent with chronic mastoiditis.

The patient was placed on a two-week course of amoxicillin-clavulanate, 500 mg every eight hours, and ciprofloxacin, 500 mg twice a day. He showed clinical improvement in his signs and symptoms in the ensuing weeks. Three weeks later, the patient presented with facial pain and right seventh nerve paralysis; magnetic resonance imaging showed a nasopharyngeal mass that on biopsy was a B-cell lymphoma. The patient declined radiation therapy and died two months later.

Patient 2

The patient, a 36-year-old HIV-positive woman, was admitted to Thomason Hospital for gradually worsening right ear pain beginning one day before admission. The patient described the pain as a stabbing pressurelike sensation in her ear and mastoid region, but did not have any discharge, tinnitus, or hearing loss. She also had a generalized headache with intermittent sensations of disequilibrium, nausea, and fever with chills. The patient was diagnosed with HIV infection 14 months before this admission, and her most recent $CD4^+$ count was 84×10^6 per liter (84 cells per µl). Since being diagnosed with HIV, she has had several episodes of acute sinusitis and right otitis media. Her medications at the time of admission included didanosine, trimethoprim-sulfamethoxazole, and acyclovir.

On physical examination, the patient's temperature was 41.1°C (106.0°F), her blood pressure was 115/65 mm per mercury, her pulse rate was 125 beats per minute, and respirations were 18 per minute. She had a bulging and injected right tympanic membrane with obliteration of the bony structures. An air-fluid level behind the tympanic membrane was not discernible, and no perforation was present. The external auditory meatus and mastoid region were tender to palpation, but no gross anatomic deviations or swelling was evident. The leukocyte count was 4.27×10^9 per liter (4,270 per µl) (0.68 neutrophils, 0.09 band forms, 0.21 lymphocytes, and 0.02 monocytes) and the cerebrospinal fluid showed a leukocyte count of 8×10^6 per liter (8 per µl) with no organisms present. Cultures done of tympanocentesis, cerebrospinal fluid, and blood specimens were all sterile, and the results of the rest of the laboratory workup were unremarkable.

The patient was diagnosed with recurrent otitis media and mastoiditis and treated with ticarcillin and clavulanate, 3.1 grams intravenously every six hours. A marked improvement was noted by the ninth hospital day, and she was discharged home with a two-week course of ceftazidime, 2 grams given intravenously every twelve hours. Following discharge, the patient's condition remained stable for two months when she had the abrupt onset of right ear pain, fever, and signs of sepsis. A computed tomographic scan of the head revealed clouding of the right mastoid air cells, and culture of the middle ear fluid grew *S pneumoniae*. A right mastoidectomy was performed without complications. The patient received intravenous ceftriaxone sodium, 1 gram intravenously every 24 hours for the following 10 days, and her condition gradually improved. Two months later, she presented with anemia and neutropenia and was ultimately diagnosed with B-cell non-Hodgkin's lymphoma, presenting as an abdominal mass. Studies were not performed to look specifically for a nasopharyngeal mass. She died two months after the diagnosis of lymphoma.

Discussion

Acute mastoiditis usually follows an episode of acute suppurative otitis media, with the pathologic events being, first, obstruction and sequestration of infection at the additus ad antrum and the smaller air cell tracts and, then, temporal or mastoid bone remodeling followed by bone resorption and decalcification.[1]

The pathogenesis of chronic mastoiditis is similar to that of acute disease, with obstruction of the eustachian tube being a more prominent feature.[1,3,5,6,8] The causal agents are usually bacterial with *S pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and occasionally anaerobes being isolated most frequently.[1,4,3,9]

In patients with AIDS, however, alterations in normal immune function and middle ear anatomy may play a role in the development of middle ear infections, including mastoiditis. The most consistent finding is poor eustachian tube function due to such factors as HIV-related adenoidal hyperplasia and hypertrophy, recurrent respiratory tract viral infection, viral-induced allergy, and nasopharyngeal masses.[3,5,6,8] Patients with HIV infection also have measurable B-cell dysfunction, neutrophil dysfunction, spontaneous B-cell proliferation with a nonspecific polyclonal increase in immunoglobulin G secretion, and a failure to respond to a variety of de novo antigenic stimuli.[7]

Several studies have described the histopathologic findings in the temporal bones of patients infected with HIV and who have AIDS.[2,10,11] Michaels and co-workers noted histologic evidence of severe otitis media in 20% of patients studied and low-grade otitis media in 60% of their patients.[2] Although they noted no clinical cases consistent with mastoiditis, radiographs of microslides indicated markedly increased density of mastoid bone and a diminished number of air cells.[2] Haversian systems were found to be highly irregular in pattern in a number of specimens.[2] Davis and associates studied the temporal bones of 13 patients with AIDS and found histologic evidence of acute otitis media in 4 patients (31%), chronic otitis media in 2 patients (15%), and serous otitis media in 3 patients (23%).[10] No descriptions of disease in mastoid bones were noted. In contrast to these studies, the histopathologic changes described by Chandrasekhar and colleagues were significant in that 7 of the 8 bone specimens analyzed demonstrated some form of petromastoiditis.[11] Two of the studies were of the temporal bones of patients with documented AIDS,[2,10] and the third was of HIV-positive patients not described as having AIDS.[11] In our review of the literature, we found accounts of 12 patients with HIV infection or AIDS and mastoiditis.[3,5,12–16] Although the incidence of mastoiditis has decreased over the past several decades,[1,17] no objective data exist on the incidence or prevalence of the disease in patients with AIDS. Information regarding the frequency rate of complications, responses to therapeutic intervention, and prognostic implications of mastoiditis in AIDS patients is also lacking. Of note, the two patients presented here followed different courses, with one responding well to standard antibiotic therapy and long-term sequelae developing in the other that ultimately required surgical therapy.

That both patients had B-cell non-Hodgkin's lymphoma is also important because a nasopharyngeal mass may have contributed to the pathogenesis of their disease. Carbone and co-workers retrospectively studied 82 patients with HIV-related non-Hodgkin's lymphoma.[18] Of the 82 patients, 15 (21%) had primary head and neck and 13 (18%) had systemic head and neck non-Hodgkin's lymphoma. Of 15 patients with primary head and neck disease, 7 (47%) presented with extranodal disease in the absence of any demonstrable disease in the lymph nodes; 11 patients (73%) had involvement of the Waldeyer's ring; 5 patients (33%) had involvement of the head and neck soft tissue; 3 patients (20%) each had involvement of the maxillary region (gum of the maxillary sinus and bones) and palate; 2 patients (13%) each had involvement of the hypopharynx, gum, and skin; and 1 patient (7%) had involvement of the epiglottis, uvula, floor of the mouth, parotid, orbit, hyoid bone, and retromolar trigone. From the clinical point of view, the stage distribution was the only statistically significant difference in the two groups (primary head and neck versus systemic head and neck non-Hodgkin's lymphoma) of the head and neck lymphoma ($P<.001$). Of 15 patients with primary head and neck non-Hodgkin's lymphoma, 10 (67%) had stages I and II, whereas all the patients with systemic head and neck non-Hodgkin's lymphoma had stages III and IV.

Shapiro and colleagues described 20 patients with AIDS in whom non-Hodgkin's lymphomas developed in the head and neck region.[19] The tumor was observed in a variety of sites, including the nasopharynx, orbit, parotid, maxillary sinus, submandibular triangle, anteri-

or and posterior cervical triangles, supraclavicular fossa, and the hypopharynx. Nine cases of oral non-Hodgkin's lymphoma occurring in homosexual male HIV-infected patients were evaluated by Green and Evasole.[20] The lymphomas were located in the maxillary or mandibular gingiva (3 patients), palate (2 patients), mandible, lateral tongue, tonsillar pillar, and retromolar pad. Carbone and associates concluded in their study that head and neck non-Hodgkin's lymphoma in HIV-infected patients represents a significant proportion (39%) of the HIV-related lymphomas.[21] Most patients with head and neck non-Hodgkin's lymphoma had severe immunodeficiency, extranodal disease, aggressive histologic findings, and a poor treatment response.[21–23]

The two cases reported here underscore the importance of being aware of mastoiditis in a patient with AIDS. That both patients also had lymphoma suggests that this association may not be casual; clinicians should keep lymphoma and an occult nasopharyngeal mass in mind when seeing HIV-infected patients who present with mastoiditis.

REFERENCES

1. Nadol JB Jr, Eavey RD. Acute and chronic mastoiditis: clinical presentation, diagnosis, and management. Curr Clin Top Infect Dis 1995; 15:204–229

2. Michaels L, Soucek S, Liang J. The ear in the acquired immunodeficiency syndrome: I. temporal bone histopathologic study. Am J Otol 1994; 15:515–522

3. Lalwani A, Sooy CD. Otologic and neurotologic manifestations of acquired immunodeficiency syndrome. Otolaryngol Clin North Am 1992; 25:1183–1195

4. Madriz J, Herrera G. Human immunodeficiency virus and acquired immune deficiency syndrome AIDS-related hearing disorders. J Am Acad Audiol 1995; 6:358–364

5. Kohan D, Rothstein SG, Cohen NL. Otologic disease in patients with acquired immunodeficiency syndrome. Ann Otol Rhinol Laryngol 1988; 97(6 pt 1):636–639

6. Sooy CD. The impact of AIDS on otolaryngology-head and neck surgery. Adv Otolaryngol Head Neck Surg 1987; 1:1–28

7. Verghese A, al-Samman M, Nahhan D, Naylor AD, Rivera M. Bacterial bronchitis and bronchiectasis in human immunodeficiency virus infection. Arch Intern Med 1994; 154:2086–2091

8. Haddeingh R, Tange R, Danner S, Schattenkerk J. Otorhinolaryngological findings in AIDS patients: a study of 63 cases. Arch Otorhinolaryngol 1987; 244:11–14

9. Rodriguez Barradas MC, Musher DM, Hamill RJ, Dowell M, Bagwell JT, Sanders CV. Unusual manifestations of pneumococcal infection in human immunodeficiency virus-infected individuals: the past revisited. Clin Infect Dis 1992; 14:192–199

10. Davis LE, Rarey KE, McLaren LC. Clinical viral infections and temporal bone histologic studies of patients with AIDS. Otolaryngol Head Neck Surg 1995; 113:695–701

11. Chandrasekhar SS, Siverls V, Sekhar HK. Histopathologic and ultrastructural changes in the temporal bones of HIV-infected human adults. Am J Otol 1992; 13:207–214

12. Gherman CR, Ward RR, Bassis ML. *Pneumocystis carinii* otitis media and mastoiditis as the initial manifestation of the acquired immunodeficiency syndrome. Am J Med 1988; 85:250–252

13. Strauss M, Fine E. Aspergillus otomastoiditis in acquired immunodeficiency syndrome. Am J Otol 1991; 12:49–53

14. Shepp DH, Tang IT, Ramundo MB, Kaplan MK. Serious *Pseudomonas aeruginosa* infection in AIDS. J Acquir Immune Defic Syndr 1994; 7:823–831

15. Linstrom CJ, Pincus RL, Leavitt EB, Urbina MC. Otologic neurotologic manifestations of HIV-related disease. Otolaryngol Head Neck Surg 1993; 108:680–687

16. Kohan D, Hammerschlag PE, Holliday RA. Otologic disease in AIDS patients: CT correlation. LaryngoscopeOtologic Disease and AIDS 1990; 100:1326–1330

17. Chui R. Otitis media. Common Problems of the Head and Neck Region 1982; 9:211–225

18. Carbone A, Vaccher E, Barzan L, Gloghini A, Volpe R, De Re V, et al. Head and neck lymphomas associated with human immunodeficiency virus infection. Arch Otolaryngol Head Neck Surg 1995; 121:210–218

19. Shapiro AL, Shechtman FG, Guida RA, Kimmelman CP. Head and neck lymphoma in patients with the acquired immune deficiency syndrome. Otolaryngol Head Neck Surg 1992; 106:258–260

20. Green TL, Eversole LR. Oral lymphomas in HIV infected patients: association with Epstein-Barr virus DNA. Oral Surg Oral Med Oral Pathol 1989; 67:437–442

21. Carbone A, Tirelli U, Vaccher E, Volpe R, Gloghini A, Bertola G, et al. A clinicopathologic study of lymphoid neoplasias associated with human immunodeficiency virus infection in Italy. Cancer 1991; 68:842–852

22. Knowles DM, Chamulak GA, Subar M, Burke JS, Dugan M, Wernz J, et al. Lymphoid neoplasia associated with the acquired immunodeficiency syndrome (AIDS): the New York University Medical Center experience with 105 patients (1981-1986). Ann Intern Med 1988; 108:744–753

23. Lowenthal DA, Straus DJ, Campbell SW, Gold JW, Clarkson BD, Koziner B. AIDS-related lymphoid neoplasia: the Memorial Hospital experience. Cancer 1988; 61:2325–2337

Medical Informatics

The Benefits and Challenges of an Electronic Medical Record: Much More than a "Word-Processed" Patient Chart

WALTER V. SUJANSKY, MD, PhD, *Palo Alto, California*

The electronic medical record (EMR) will constitute the core of a computerized health care system in the near future. The electronic storage of clinical information will create the potential for computer-based tools to help clinicians significantly enhance the quality of medical care and increase the efficiency of medical practice. These tools may include reminder systems that identify patients who are due for preventative care interventions, alerting systems that detect contraindications among prescribed medications, and coding systems that facilitate the selection of correct billing codes for patient encounters. Numerous other "decision-support" tools have been developed and may soon facilitate the practice of clinical medicine. The potential of such tools will not be realized, however, if the EMR is just a set of textual documents stored in a computer, i.e. a "word-processed" patient chart. To support intelligent and useful tools, the EMR must have a systematic internal model of the information it contains and must support the efficient capture of clinical information in a manner consistent with this model. Although commercially available EMR systems that have such features are appearing, the builders and the buyers of EMR systems must continue to focus on the proper design of these systems if the benefits of computerization are to be fully realized.

(Sujansky WV. The Benefits and Challenges of an Electronic Medical Record: Much More than a "Word-Processed" Patient Chart. West J Med 1998; 169:176-183)

It is all but a truism today that health care is among the last major industries to "computerize," and that the "computerization" of health care is an inevitable trend, driven by the need to improve productivity, assure and demonstrate quality, integrate organizations, facilitate research, and better manage the health-care process.[1] However, there is much less agreement on what exactly computerization *means* in the context of health care and what a computerized health-care world will look like. This lack of clarity is especially true with respect to the primary medical record, i.e. "the chart." The primary medical record constitutes the source and core of the clinical information to be computerized, and the nature of its rendition in a computer-processible form will influence, more than any other factor, the benefits or the headaches of a computerized health-care system.[2]

The potential benefits of computerization to individual clinicians and to healthcare organizations are considerable: Computer-based systems can generate reports of patients due for mammography, cholesterol screening, and many other preventative measures; programs can quickly identify patients taking medications that have been recalled or for which monitoring procedures have changed; alerting systems can immediately notify clinicians when laboratory or other test results indicate adverse conditions in a patient that require prompt attention; computerized practice guidelines can help clinicians plan diagnostic and treatment strategies in accordance with selected guidelines, or warn clinicians when their interventions are straying from a guideline; drug-monitoring programs can identify contraindications based on drug-drug interactions and therapeutic overlap with existing medications; computerized coding systems can suggest the most appropriate billing codes for encounters based on the scope and nature of clinical documentation; researchers can analyze large sets of electronic patient data to quickly and cost-effectively conduct retrospective clinical studies.

All of the computer-enabled functionalities listed above have been demonstrated in medical-computing research settings, but very few exist in routine clinical settings. One important reason for this lack of widespread adoption is the absence or inappropriate representation of the primary medical record in a computer-

From Oceania, Incorporated, Palo Alto, California.
Reprint requests to Walter V. Sujansky, MD, PhD, Oceania, Inc., 3145, Porter Dr, Suite 103, Palo Alto, CA 94304.

processible form. This article describes numerous computer programs in use today that effectively and unobtrusively assist in clinical decision making by analyzing electronic medical records (EMRs). The article also discusses the features of EMRs that such programs require and why these features are uncommon. The next section reviews several types of computer programs that have proven clinically effective and that depend on appropriate representations of clinical data in EMR systems. The following section briefly describes the characteristics of effective EMR systems and one of the technical challenges that impedes the widespread availability of such systems.

Clinical Computer Tools that Require Electronic Medical Records

Several clinical institutions around the country have sophisticated electronic medical record systems. These include (though are not limited to) Columbia Presbyterian Medical Center in New York, The Latter-Day Saints Hospital in Salt Lake City, The Regenstrief Institute in Indianapolis, and several Harvard teaching hospitals in Boston. These institutions and others have deployed a variety of useful computer-based tools that are integrated with and depend on clinical data stored in their EMRs. There are several classes of such tools.

Clinical Event Monitors.

Clinical event monitors are computer programs that look for combinations of clinical data that indicate the presence of adverse and noteworthy clinical situations.[3] The situations are typically ones that busy caregivers might otherwise overlook or discover only after an inappropriate delay. For example, several hours might pass in a busy hospital between the time a low serum potassium value is reported for a patient on digoxin and the time a clinician reviews the laboratory results. Clinical event monitors can recognize such combinations of data immediately and at any time (for example, right after a lab value is electronically reported). When the programs detect adverse situations, they generate and dispatch alert messages to appropriate personnel, apprising them of the problem and possibly suggesting ameliorative actions. The method of dispatching a message depends on the urgency of the alert; for example, a covering physician might be paged in response to a critical lab value. A number of studies have shown that clinical event-monitoring systems can be effective in improving patient care in hospital settings.[4–7]

It is obvious that clinical event monitors require access to clinical data of various kinds, such as vital signs, laboratory results, radiology reports, current medications, problem lists, and past medical histories. The electronic medical record is the most comprehensive repository of such data, but the data must be organized and structured in such a way that the event monitors can identify the clinical situations of interest reliably and efficiently. Poorly structured representations of the medical record, such as those found in "word-processed" patient charts, result in false-positive and false-negative clinical alerts. At a certain threshold, the rate of false positive and negative alerts becomes unacceptable and clinicians perceive the event monitors as annoyances, at best, and incompetent, at worst.

Preventative Care Recommendations.

Related to clinical event monitors, preventative care recommendation systems identify patients who are eligible and due for various preventative care interventions, such as screening tests, vaccinations, and patient counseling. Such systems are valuable, particularly in outpatient settings, where individual clinicians may be responsible for hundreds of patients, many of whom infrequently seek care. Recommendation systems can also help clinicians stay abreast of frequent changes and variations in the preventative care guidelines published by authoritative sources, such as the American Heart Association and American Cancer Society. The systems can help clinicians select the desired guidelines and identify patients who fit those guidelines. At least one study has shown that physician compliance with certain guidelines increases through the use of a preventative care prompting system integrated with an electronic medical record. [8]

The criteria for preventative interventions usually include demographic data such as age and gender, the existence of risk factors, the absence of exclusionary criteria, and the time interval since previous interventions. These data are usually available in the paper chart, and should be included in a structured form in the EMR. As with clinical alerts, preventative care recommendation systems must identify relevant criteria with sufficient accuracy to prevent false-positive and false-negative recommendations. An appropriate internal model of clinical data is essential to this objective.

Diagnostic Decision Support Programs.

Diagnostic decision-support programs generate differential diagnoses based on clinical findings and medical knowledge bases. The findings, which may include historical, physical, and laboratory findings, are typically entered by the users of such systems. The knowledge bases relate findings to diseases, usually in some probabilistic fashion, and rank the set of diseases suggested by a constellation of findings. Among the most prominent of these systems are programs that provide diagnostic assistance in the fields of infectious disease[9] and general internal medicine.[10–12] The diagnostic acumen of these programs has been studied and the systems have proven most useful in suggesting relevant diagnoses that clinicians would have otherwise failed to consider (rather than in ranking diagnoses more effectively than clinicians).[13] Most of the programs allow users to inspect the knowledge bases and thereby learn which findings they should pursue to rule in or rule out the (presumably less common) additional diagnoses. These capabilities unto themselves can be very

useful to primary care physicians, who are increasingly asked to manage a broader set of medical conditions and patient presentations.[14] For example, many primary care physicians confronted with an intensely pruritic lower-extremity rash may overlook the possibility of cutaneous larva migrans (CLM) and fail to elicit the appropriate travel history needed to suggest or rule out this rare but uncomfortable infection.[15] In a recent study, 58% of Canadian patients with CLM eventually referred to a tropical disease unit were misdiagnosed and ineffectively treated prior to seeking specialty care.[16] Diagnostic decision-support systems could assist non-specialist clinicians in such cases.

Although diagnostic decision-support programs have been shown to be useful and effective, very few are in common use today. One significant reason for this is the extra effort required to consult such a system at the time it is needed. Given current medical record systems, the clinician still must manually enter the set of findings for each patient into the system, although she has already documented the same findings in the patient record. Without an internal model of clinical data, including a model of all relevant findings, there is no way to effectively "link" the patient record to diagnostic decision-support programs such that onerous and redundant data entry is avoided. Although researchers have integrated decision-support programs with electronic medical record systems in a few settings,[17,18] until such links are widely established and decision-support is widely enabled with the single click of a button, it is unlikely that busy clinicians will avail themselves of the benefits of diagnostic decision-support programs.

Automated Practice Guidelines.

As described in a recent article in this series, clinical practice guidelines have enormous potential to improve quality and accountability in health care, but their deployment and use remains sufficiently difficult as to limit their effectiveness.[19] Specifically, current paper-based practice guidelines and paper-based medical records require that clinicians find the appropriate guideline(s) that apply to their patients and determine if the clinical conditions required to trigger diagnostic and treatment actions in those guideline(s) are present. Given the multitude and complexity of guidelines, both of these steps are time consuming, information intensive, and, for many clinicians, prohibitive. Automated practice guidelines are distinct from paper-based guidelines in that they are represented as computer programs and they are linked to EMR systems.[20–22] These features may allow clinicians more easily to select the guidelines they wish to use, access the information in those guidelines, determine if the guidelines apply to their patients, and determine what actions the guidelines recommend for their patients.

The advantages of automated practice guidelines rely on the electronic representation of clinical data that the guidelines need. For example, recommendations regarding cardiac revascularization for patients with unstable angina are conditioned on symptom severity, physical signs, response to prior medical treatment, the presence of comorbidities, and the results of cardiac catheterization, echocardiography, and electrocardiography.[23] All of these data, which are typically recorded in the paper record, must be completely and precisely represented in the electronic medical record to support "automation" of practice guidelines.

Drug-prescription Assistance.

One of the most mature areas of computerized decision support in health care is drug-prescription assistance. Several commercial systems exist that can detect drug-drug, drug-allergy, drug-disease, and drug-lab test interactions based on prescription information and other clinical data.[24–26] Certain of these systems can also assist in appropriately dosing medications, identifying therapeutically overlapping medications, and detecting patient non-compliance. Drug-prescription assistance may be one of the most important areas of computerized decision support, in terms of clinical and economic outcomes. A recent study estimated that the morbidity and mortality related to medication problems cost over $76 billion per year in the ambulatory setting in the United States, roughly 8% of total health care spending.[27] The study also estimated that up to half of the medication problems, which include adverse drug reactions, inappropriate drug selections, inappropriate dosing, and patient non-compliance, are preventable.

Currently, most drug-prescription assistance programs are used by pharmacists. In the outpatient setting, however, community pharmacists have limited access to the data that drive drug-prescription assistance, such as patients' existing medications, diagnoses, and allergic histories. Because these data are typically documented in the medical record, the optimal location of drug-prescription assistance systems may be in the physician's office, as integrated parts of clinical information systems. Such information systems would include an electronic medical record, an order-entry capability to capture drug prescriptions, and a drug-prescription assistance component. To support the requisite links between the drug-prescription component and the EMR component, a sufficient internal model of the relevant medication, diagnosis, and allergy information in the EMR is required.

Billing Codes.

A common annoyance for clinicians and administrators in the ambulatory setting is the need to assign appropriate billing codes for each outpatient encounter. These codes, which specify diagnoses, interventions, and the general scope of an encounter, are required by the Health Care Financing Administration, Medicaid, and most private insurers. Not only is the assignment of billing codes a time-consuming and mundane task, but it is often done incorrectly, which may needlessly reduce or delay reimbursements or trigger audits by payers. Many individual clinicians and certain organi-

zations have developed flow sheets or rules to assist in the task of assigning billing codes based on the clinical elements of an encounter. For example, a billing rule may specify that a Level-3 encounter should be billed for a new patient if at least four components in the history-of-present-illness are documented, between two and nine systems are reviewed, and an extended exam of the affected body area or organ system is performed. Another rule may specify that the ICD-9 diagnosis code "443.9" (Intermittent Claudication) may be used if there is pain and weakness of the affected limb during use, but NOT if the cause of the symptoms is known to be atherosclerosis, in which case the diagnosis code "440.20" (Atherosclerosis of the Extremities) should be used.

As with practice guidelines, matching such rules to the specifics of an individual patient may be time consuming and information intensive. Given that the bulk of information driving these rules is directly available in the clinical record, computer-based tools can facilitate the selection of appropriate billing codes. One study found that a computer-based coding tool integrated with an EMR increased the accuracy of diagnosis coding by 31% and reduced coding time by 50%.[28] It is not surprising that the ability of such tools to improve coding and save time depends on the appropriate modeling of information in the electronic medical record. Until the EMR contains systematically structured clinical data, tools to streamline and improve the coding process will have limited utility.

Bibliographic Retrieval Systems.

During the routine course of clinical care, many questions arise regarding the proper management of patients. What is the predictive value of the test I am ordering? What is the latest treatment for this condition? Can any of the patient's medications be causing this new symptom? Studies have shown that most of these questions go unanswered at the time management decisions are made, and that the sources of information for the answered questions are usually colleagues rather than definitive references, such as text books and journals.[29,30] At the same time, bibliographic retrieval systems that allow searching of the medical literature, such as Medline, and bibliographic retrieval systems that provide full-text access to journal articles, such as BRS Online, are becoming increasingly common and affordable. Although the medical literature is not the appropriate resource for all clinical questions, studies have shown that searching the literature from clinical settings is feasible and does affect clinical decision making.[31,32] Nevertheless, physicians cite bibliographic retrieval systems as the least desirable sources of information in clinical settings, largely because the systems are perceived as time consuming, difficult to use, and bereft of clinically relevant information.[30] This perception is not surprising given that inexperienced Medline users miss many relevant citations and search inefficiently compared to expert users.[31]

Several researchers have attempted to address the incongruence between the usefulness and the use of bibliographic retrieval systems by facilitating bibliographic searching through intelligent computer-based tools linked to EMRs. One such tool maps patients' diagnosis and procedure codes from a hospital information system to the Medical Subject Heading (MeSH) terms used to index Medline citations.[33] The tool uses the generated MeSH terms, along with one of several general information requests that the user has selected, to automatically formulate and submit a Medline search that is specific to the patient and the clinician's information need. This smooth integration of the Medline search capability with an electronic medical record relieves the clinician from remembering how to connect to Medline and how to formulate a potentially complex search request. These gaps in computer skills, and the attendant discomfort they cause, may well be the impediments standing between many information needs and the resources already available to meet them. As electronic medical records are extended to include a greater variety of structured clinical information (in addition to diagnoses and procedures), bibliographic retrieval tools will likely become more powerful, easy to use, and widely accepted.

Clinical Research Tools.

Most retrospective clinical research is still conducted today through laborious manual chart reviews done by medical students, research assistants, and office staff. This method of research is necessary because most clinical data are still locked in reams of paper charts. It is obvious that a rigorously modeled and well structured EMR could change this situation dramatically. Instead of poring over chart after chart, researchers could write programs to search and statistically analyze electronic databases of patient records without ever leaving their offices. The "word-processed" patient chart does not support this model of research, however, because the clinical information within it is not consistently represented and therefore not amenable to automated aggregation, comparison, and statistical analysis. The data in "word-processed" patient charts still must be extracted and abstracted into a normalized form before one can use the data for research. The internal model of a true EMR, however, already represents clinical data in a normalized form and can directly support clinical research.

Investigators have exploited this property of true EMRs to conduct several interesting studies with relatively minimal effort and expense. Tierney, et. al., used routine data from a comprehensive EMR system to identify predictors of mortality among patients with reactive airway disease (RAD).[34] Out of 90 potentially predictive variables recorded in the EMR, the study identified eight statistically significant predictors of death among RAD patients (the most strongly predictive was concomitant heart failure). The authors suggest that knowledge of grave risk factors among RAD patients can help practitioners direct healthcare resources, such as referrals to

pulmonary subspecialists, close monitoring, and aggressive preventative care measures, toward the patients at highest risk, thereby improving the average outcome for this population. Evans, et al, conducted a similar study at a different institution to identify risk factors for nosocomial infections among hospitalized patients.[35] These studies underscore the feasibility of conducting clinical research based on data in EMR systems and the value of carefully coding and structuring clinical data to support such research.

Effective Representations for the Electronic Medical Record

Researchers have demonstrated the effectiveness of clinical decision-support tools in settings where clinical data is available in electronic databases. The mere storage of clinical documents in a computer, however, is not sufficient to enable decision-support tools. To provide a "data substrate" for reliable and efficient decision-support tools, the electronic representation of primary clinical data must conform to certain specific design criteria, which together define a "true" electronic medical record.

Among the possible renditions of the primary medical record in a computerized form, one can imagine, at one extreme, a system in which all clinical information continues to be recorded on paper and maintained in record rooms, but the individual sheets of paper are scanned (i.e. digitally photographed) into a computer database and indexed by patient name, medical record number, and so forth. During routine care, clinicians use a computer to access these "pictures" of the medical record, instead of accessing the physical paper chart. New information is handwritten or typed on paper sheets, which are subsequently scanned into the database and ultimately filed in the paper chart. The rendition of the medical record as a set of scanned images in a computer database is useful because it minimizes the chance that the record will be unavailable, allows multiple parties to access the record concurrently, and facilitates the transmission of the record to various locations, all without requiring clinicians to change their current charting behavior. Systems such as this exist today,[36,37] but are they true EMRs?

The "word-processed" patient chart.

A natural enhancement to the medical record system just described entails that clinical information is not only stored but also *captured* using a computer. Clinical notes, orders, problem lists, and discharge summaries are directly typed by clinicians or transcribed from dictations into the computer database, circumventing the scanning step. This enhancement not only reduces the time before the clinical information is available in the database, but allows text-based searching tools to locate words and phrases of interest in the medical record (such as "family history of CAD"). The electronic capture of clinical information as collections of organized and indexed textual documents results in a "word-processed" patient chart, because such a rendition of the medical record is similar to that generated using a word processor. Most commercially available computer-based patient record systems today provide this rendition, but is this a true electronic medical record?

There is a growing realization that the word-processed patient chart is *not* a true electronic medical record. It is not an electronic medical record, in general, because it cannot support the needs that are driving computerization in health care, namely improving productivity, assuring and demonstrating quality, integrating organizations, and facilitating research. Specifically, the word-processed patient chart cannot support these needs because it lacks a comprehensive *internal model* of the clinical information that it contains. In the vernacular of medicine, there are many ways to express the same meaning with respect to terminology and the grammatical construction of phrases and sentences (e.g. "dyspnea" versus "SOB," and "no splenomegaly" versus "splenomegaly not appreciated" versus "spleen normal," and so forth). In addition, the same words or phrases may express different meanings, depending on their context ("erythromycin" appearing in the "Allergies" section of a clinical note has a dramatically different meaning than "erythromycin" appearing in the "Prescription" section). In the word-processed patient chart, the complete universe of medical utterances may appear, and no consistent internal model exists of how clinical information is represented. This method of documentation makes it exceedingly difficult for computer-based tools to monitor, search, analyze, and compare clinical data with intelligence or reliability. In short, computer-based tools cannot *understand* clinical information in the absence of an internal model, and without an understanding, the tools cannot produce results that we consider sensible, useful, and trustworthy.

Internal Models of Clinical Information.

What constitutes an internal model of clinical information that computers can "understand?" (*internal* refers to the level at which information is stored inside the computer, not necessarily the level at which information is seen by users of the computer). There are two important elements to such a model:

- Internal representations of data that are *concept based*, not word based
- Internal representations of the *contexts* in which data are recorded

Concept-based representation means that medical concepts are stored as unique codes or identifiers that have no intrinsic meanings, but which are assigned agreed-upon conceptual meanings. For example, the code "F20040" may be assigned the conceptual meaning "the symptom of dyspnea." This code provides a unique representation of the concept "symptom of dyspnea" that is independent of the actual textual representation(s) that may be used to enter or display that concept. The textual representation seen by users of the computer may, in fact, be "dyspnea," "dyspneic,"

"SOB," or "shortness of breath" (or any other textual representation that has been registered as a synonym for the concept "F20040"). Concept-based representation allows a computer program that must know if a patient reported dyspnea to search the medical record only for the code "F20040." Word-based representation, on the other hand, provides no agreed-upon code or text that uniquely represents the meaning "symptom of dyspnea." Hence, a computer program must search the medical record for numerous possible words or phrases that may represent the concept "dyspnea." There is no guarantee that the program will anticipate all of the possible ways the concept may be represented (e.g. "dysp."). Furthermore, the computer program must be smart enough to exclude target words that appear in negation phrases such as "no dyspnea" or "patient denies dyspnea," a notably difficult task.[38] Lastly, computer programs that search for words in documents rather than for codes in databases are much less efficient and much slower.[39]

The internal models of effective EMR systems must represent not only individual clinical concepts, but also the contexts in which those concepts are recorded. Context representation is necessary to fully and correctly capture the intended meaning of documented clinical information. For example, the clinical concept "reactive airway disease" documented in the context of "Family History" has a different meaning and implies different diagnostic and therapeutic strategies than the same concept documented in the context of "Assessment." It is obviously important for computer programs that automate clinical guidelines, double check drug prescriptions, or suggest appropriate billing codes to distinguish the two meanings. Sophisticated EMR systems have extensive models of contexts that are relevant to the capture of clinical information.[40,41]

The Challenge of Capturing Structured Information

Powerful EMR systems that store data for decision-support programs must represent clinical information in a systematically structured format. Because the clinician is the source of most information in the medical record, a requirement of powerful EMR systems is the ability to capture structured information directly from clinicians. However, this has proven very difficult. Capturing information in a structured format requires clinicians to *select* appropriate codes from a fixed set of coded clinical concepts and to *place* these codes in predefined clinical contexts. Most clinicians, however, are accustomed to *generating* clinical information by writing, typing, drawing, or dictating the observations that they wish to record. Relative to generating clinical narratives, selecting coded concepts requires more time because it entails a search through the set of all concepts for the desired observations. In the busy practice environments that characterize medicine today, delays and inefficiencies introduced by a technology will discourage the adoption of that technology, regardless of the additional benefits that it may confer.[42] Researchers in medical computing are addressing the problems of data capture by pursuing two distinct strategies: structured data entry and natural language processing.

Structured Entry.

Structured data entry entails the capture of information from the clinician directly in the coded format needed by the EMR. The proponents of structured data entry work to build well-designed and intelligent user interfaces that minimize the time and effort required to capture information in this way. Their strategies include using medical knowledge to anticipate the concepts that clinicians wish to record[43,44] and designing input screens that allow clinicians to locate desired concepts quickly.[45] For example, user interfaces that apply medical knowledge know to present additional options that record the dosage and frequency of the concept "Penicillin" when "Penicillin" is selected as a prescription, but to suppress these options when "Penicillin" is selected as a drug allergy. Other user-interface research has revealed that clinicians find specific concepts more quickly when those concepts appear consistently in the same position on the computer screen.[45]

Language Processing.

Natural language processing (NLP) is the alternative to structured data entry. NLP entails the capture of information from the clinician in an unstructured narrative format, and the subsequent *extraction* of structured clinical concepts by automated computer tools. The narrative text may be typed in by the clinician or it may be dictated and transcribed. The proponents of natural language processing work to build programs that can scan narrative documents and recognize relevant clinical concepts with high accuracy. Once such concepts are recognized, they are translated to concept-based codes and placed in their appropriate contexts in the EMR. Issues in building NLP programs include specifying sufficiently large vocabularies to recognize all of the terms, acronyms, and abbreviations typically used in clinical documents, and designing sufficiently powerful algorithms to recognize all of the grammatical forms in which positive and negative findings may be expressed in clinical documents. Natural language processing of medical narratives has demonstrated impressive performance for limited document types (such as radiology reports, surgical reports, and discharge summaries), providing upwards of 90% sensitivity and specificity of concept identification.[46–48] However, no NLP systems have yet shown the ability to extract all clinically relevant information from all document types that may appear in the medical record. Although it is not clear whether structured data entry or natural language processing (or some hybrid of the two) is the superior strategy for capturing concept-based data in EMRs, it is likely that further research is needed before either method proves adequate.

Other Challenges.

This article has focused on the technical issues related to the capture and representation of clinical information in EMR systems. However, many non-technical issues also must be resolved before powerful EMR systems can become realities in our health care system. These include issues of patient privacy and confidentiality, physician acceptance of closer scrutiny by management, regulatory and medicolegal standards for electronic medical records, and cost-benefit justification for investments in EMR systems. All of these technical, cultural, and economic challenges must be met before the benefits offered by EMRs will be available widely.

Summary

Electronic medical record (EMR) systems have the potential to significantly improve the way that clinical information is handled and clinical medicine is practiced, to the point of constituting a revolutionary technology in health care. However, poorly designed "word-processed" EMRs will deliver on very few promises of a computerized health care system. Without well-designed internal models of the clinical information that they store, EMRs will lock patient data in electronic files, much the way that data are locked in paper charts today. Isolating clinical information from the computer-based tools that could monitor, search, analyze, compare, and aggregate it will deprive clinicians of most benefits that computer technology can confer. Recognizing this, the builders of EMR systems must continue to develop proper representations of clinical information and the consumers of EMR systems must continue to insist on products with the appropriate design and functionality.

REFERENCES

1. U.S. Congress, Office of Technology Assessment. Bringing Health Care Online: The Role of Information Technologies, OTA-ITC-624. Washington, DC: U.S. Government Printing Office, September 1995

2. Dick RS, Steen EB. The Computer-based Patient Record: An Essential Technology for Health Care. Washington, DC: National Academy Press, 1991

3. Hripcsak G, Clayton PD, Jenders RA, Cimino JJ, Johnson SB. Design of a clinical event monitor. Comput Biomed Res, 1996 Jun, 29:3, 194-221

4. Rind DM et al. Effect of computer-based alerts on the treatment and outcomes of hospitalized patients. Arch Intern Med, 1994 Jul 11, 154:13, 1511-7

5. Evans RS, et al. Preventing adverse drug events in hospitalized patients. Ann Pharmacother, 1994 Apr, 28:4, 523-7

6. Bates DW, O'Neil AC, Boyle D, Teich J, Chertow GM, Komaroff AL, Brennan TA. Potential identifiability and preventability of adverse events using information systems. J Am Med Inform Assoc, 1994 Sep-Oct, 1:5, 404-11

7. Kuperman GJ, Teich JM, Bates DW, Hiltz FL, Hurley JM, Lee RY, Paterno MD. Detecting alerts, notifying the physician, and offering action items: a comprehensive alerting system. Proc AMIA Annu Fall Symp, 1996, 704-8

8. McDonald CJ et al. Reminders to physicians from an introspective computer medical record. A two-year randomized trial. Ann Intern Med, 1984 Jan, 100:1, 130-8

9. Buchanan BG, Shortliffe EH. Rule-Based Expert Systems: The MYCIN Experiments of the Stanford Heuristic Programming Project. Reading, MA: Addison-Wesley, 1984

10. Barnett GO, Cimino JJ, Hupp JA, Hoffer EP. DXplain. An evolving diagnostic decision-support system. JAMA, 1987 Jul 3, 258:1, 67-74

11. Miller R, Masarie FE, Myers JD. Quick medical reference (QMR) for diagnostic assistance. MD Comput, 1986 Sep-Oct, 3:5, 34-48

12. Bergeron B. Iliad: a diagnostic consultant and patient simulator. MD Comput, 1991 Jan-Feb, 8:1, 46-53

13. Berner ES et al. Performance of four computer-based diagnostic systems. N Engl J Med, 1994 Jun 23, 330:25, 1792-6

14. Butler RN, Sherman FT, Rhinehart E, Klein S, Rother JC. Managed care: new challenges, new roles for the primary care physician. 2. Geriatrics, 1996 Nov, 51:11, 35-6, 39-41, 45-6

15. Uppal A, Liebers D, Tobin EH. Tracking the itch. When to suspect migrating larvae. Postgrad Med, 1997 May, 101:5, 281-2, 288

16. Davies HD, Sakuls P, Keystone JS. Creeping eruption. A review of clinical presentation and management of 60 cases presenting to a tropical disease unit. Arch Dermatol, 1993 May, 129:5, 588-91

17. Elhanan G, Socratous SA, Cimino JJ. Integrating DXplain into a clinical information system using the World Wide Web. Proc AMIA Annu Fall Symp, 1996, 348-52

18. Wong ET, Pryor TA, Huff SM, Haug PJ, Warner HR. Interfacing a standalone diagnostic expert system with a hospital information system. Comput Biomed Res, 1994 Apr, 27:2, 116-29

19. Owens D. Use of Medical Informatics to Implement and Develop Clinical Practice Guidelines. West J Med 1998; 168:166-175

20. Safran C et al. Guidelines for Management of HIV infection with computer-based patient records. Lancet, 1995; 346

21. Loback DF, Hammond WE. Development and evaluation of a computer-assisted management protocol (CAMP): Improved compliance with care guidelines for diabetes mellitus. Proc Annu Symp Comput Appl Med Care, 1994: 787-91

22. Henderson SE et al. Computerized clinical protocols in an intensive care unit: How well are they followed? Proc Annu Symp Comput Appl Med Care, 1990: 284-8

23. AHCPR guideline for unstable angina

24. First DataBank. 1111 Bayhill Drive, San Bruno, CA 94066. http://www.firstdatabank.com

25. Medi-Span, Inc. 8425 Woodfield Crossing Bovd. Indianapolis, Indiana 46240. http://www.medispan.com

26. Multim Information Services, Inc. 3200 Cherry Creek South Drive, Suite 300. Denver, CO 80209. http://www.multum.com

27. Johnson JA, Bootman JL. Drug-related morbidity and mortality. A cost-of-illness model. Arch Intern Med, 1995 Oct 9, 155:18, 1949-56

28. Hohnloser JH, Pürner F, Kadlec P. Coding medical concepts: a controlled experiment with a computerised coding tool. Int J Clin Monit Comput, 1995, 12:3, 141-5

29. Covell DG, Uman GC, Manning PR. Information needs in office practice: are they being met? Ann Intern Med, 1985 Oct, 103:4, 596-9

30. Curley SP, Connelly DP, Rich EC. Physicians' use of medical knowledge resources: preliminary theoretical framework and findings. Med Decis Making, 1990 Oct-Dec, 10:4, 231-41

31. Haynes RB, McKibbon KA, Walker CJ, Ryan N, Fitzgerald D, Ramsden MF. Online access to MEDLINE in clinical settings. A study of use and usefulness. Ann Intern Med, 1990 Jan 1, 112:1, 78-84

32. Gorman P. Does the medical literature contain the evidence to answer the questions of primary care physicians? Preliminary findings of a study. Proc Annu Symp Comput Appl Med Care, 1993, 571-5

33. Cimino JJ, Johnson SB, Aguirre A, Roderer N, Clayton PD. The MEDLINE Button. Proc Annu Symp Comput Appl Med Care, 1992, 81-5

34. Tierney WM et al. Using Computer-based Medical Records to Predict Mortality Risk for Inner-city Patients with Reactive Airways Disease. J Am Med Inform Assoc, 1997 Jul-Aug, 313-21

35. Evans RS et al. Computerized identification of patients at high risk for hospital-acquired infection. Am J Infect Control, 1992 Feb, 20:1, 4-10

36. Moran WP et al. Implementing computerized tracking at a community health center: challenges and solutions. Proc Annu Symp Comput Appl Med Care, 1993, 139-43

37. Case Study: The Toledo Hospital Turns to Document Imaging To Automate Emergency Center Medical Records," HealthCare Telecom Report, Sept. 26, 1994, vol. 2, No. 20, pp 1, 5-7

38. Spackman KA et al. Recognizing noun phrases in medical discharge summaries: an evaluation of two natural language parsers. Proc AMIA Annu Fall Symp, 1996, 155-58

39. Lamiell JM; Wojcik ZM; Isaacks J. Computer auditing of surgical operative reports written in English. Proc Annu Symp Comput Appl Med Care, 1993, 269-73

40. Johnson S, Friedman C, Cimino JJ, Clark T, Hripcsak G, Clayton PD. Conceptual data model for a central patient database. Proc Annu Symp Comput Appl Med Care, 1991, 381-5

41. Medical Data Dictionary for Decision Support Applications. Huff SM, Craig RB, Could BL, Castagno DL, Smilan RE. Proc Annu Symp Comput Appl Med Care, 1987, 310-317

42. Kaplan B. The influence of medical values and practices on medical computer applications. In: Anderson JG, Jay SJ, eds. Use and Impact of Computers in Clinical Medicine. New York: Springer-Verlag. 1987:39-50

43. Moorman PW, van Ginneken AM, van der Lei J, van Bemmel JH. A model for structured data entry based on explicit descriptional knowledge. Methods Inf Med, 1994 Dec, 33:5, 454-63

44. Bernauer J. Conceptual graphs as an operational model for descriptive findings. Proc Annu Symp Comput Appl Med Care, 1991, 214-8

45. Poon AD, Fagan LM, Shortliffe EH. The PEN-Ivory project: exploring user-interface design for the selection of items from large controlled vocabularies of medicine. J Am Med Inform Assoc, 1996 Mar-Apr, 3:2, 168-83

46. Hripcsak G, Friedman C, Alderson PO, DuMouchel W, Johnson SB, Clayton PD. Unlocking clinical data from narrative reports: a study of natural language processing. Ann Intern Med, 1995 May 1, 122:9, 681-8

47. Lamiell JM, Wojcik ZM, Isaacks J. Computer auditing of surgical operative reports written in English. Proc Annu Symp Comput Appl Med Care, 1993, 269-73

48. Sager N, Lyman M, Bucknall C, Nhan N, Tick LJ. Natural language processing and the representation of clinical data. J Am Med Inform Assoc, 1994 Mar-Apr, 1:2, 142-60

Lessons From the Practice

The Unlikely Role Model

LINDA L. HILL, MD, MPH, *San Diego, California*

In shaky handwriting, the space next to "occupation" had been completed with the word "midwife."

I glanced up from the patient's chart to take a closer look at the gentle, 57-year-old Vietnamese woman sitting across from me. Appearing fatigued and detached, she looked an unlikely candidate for such a challenging occupation. I asked the interpreter to clarify her entry, suggesting that "housewife" and "midwife" were easily confused.

My interpreter spoke with the woman for a few minutes and told me that, just as stated, she had been a midwife in Vietnam. She was my last patient of the morning, so I indulged my curiosity and began to learn her story. The incredible saga unfolded over several visits.

Mrs. NL had indeed been a midwife for 20 years in Vietnam. She learned her profession the way health care providers did in the Western world until this century: as an apprentice, in this case to her father. Though she had not worked since the Communists shut down all nongovernment health care in Vietnam in 1975, she nonetheless continued to identify herself as a midwife.

Her clients delivered in one communal room of her home, where her practice was carried out. On busy days, she had delivered as many as 10 babies as she struggled to keep track of the women needing urgent attention. Cesarean deliveries were transferred to a hospital. Mrs. NL claimed to be well supported by the physicians in town, though sometimes her decisions to transfer a patient would be questioned. Once, in the case of a woman presenting with a breech birth, Mrs. NL had to convince a skeptical obstetrician by phone that the two legs she was seeing belonged to two different babies. Fortunately, she prevailed and the twins were successfully delivered at the hospital.

Not all problems could be anticipated or solved. Her heart would sink when a woman with syphilis came in to deliver because such babies sometimes were deformed. She delivered baby after baby with limited equipment. The American presence in Vietnam gave her access to some supplies such as disposable gloves, which she used "when there was time." Anesthesia was either intramuscular or local, injected with "boiled needles" from her own sterilizer.

However, the American presence also had its downside. Mrs. NL's clients often included Vietnamese women whose GI partners frequented a canteen near her village, which was outside of Saigon. Four of the Amerasian babies she had delivered were abandoned and left with her. She didn't know the parents' names.

Because her services were cash transactions only, without record keeping or billing, there was no way to trace the parents. Chances were slim that the families would have accepted the children even if she had found them. The more than 100,000 Amerasians left in Vietnam at the end of the war were usually thrown out on the streets to survive by begging or prostitution. Even the children who stayed with their mothers experienced discrimination at school and work, with ongoing economic hardships throughout their lives.

Mrs. NL, having 10 children of her own, was able to raise only one of the Amerasian babies. After keeping the other three a few months, she reluctantly gave them to a Catholic orphanage. The Amerasian daughter she adopted was about the age of her twin girls, her seventh and eighth children. She raised the girl as part of her family, protecting her as best she could from the harsh treatment usually given Amerasians. In 1989, Mrs. NL, her husband, and their 11 children, including the Amerasian girl, moved to San Diego. Her adopted daughter now owns her own hairdressing shop and is married with two children.

I have worked in San Diego since 1980, after training in Ottawa, Ontario and Montreal, Quebec, at a low-income community health center where the patient population includes members of the large Indochinese community. The years in Canada treating many patients who spoke neither English nor French helped prepare me for the far more daunting language hurdles I face treating the Hmong, Laotian, and Vietnamese refugees who visit our clinic. However, nothing prepared me for the emotional involvement I would feel listening to these brave and resilient people. Many of their health problems directly relate to fighting a guerrilla war, then, leaving their countries, professions, status, and families behind, striving to become good citizens in a new country.

(Hill LL. An Unlikely Role Model. West J Med 1998; 169:184–185)

From UCSD-SDSU General Preventive Medicine Residency, San Diego State University, San Diego.
Reprint requests to Linda L. Hill, MD, General Preventive Medicine Residency, 5500 Campanile Drive, San Diego State University, San Diego, CA 92182-4701.

Mrs. NL's narrative is but one of many tales of heroism told to me over the last 18 years. Yet, her story strikes a responsive chord. Her self-sacrificing involvement with the welfare of her patients encourages and inspires me. As a health care provider she braved the physical risks that each of us faces daily, but with little or no protection. Recently, she was found to be hepatitis C positive, most likely as the result of her occupation. Mrs. NL treats this health problem with the same courage she mustered in Vietnam to deal with the demands of being a midwife, to cope with abandoned babies, and finally to face the closure of her practice. I can only hope that I would respond with the same courage if confronted with such formidable challenges. I do know that I will always list "physician" as my occupation, as Mrs. NL did "midwife" 20 years after her last delivery.

Western Journal of Medicine

INSTRUCTIONS FOR AUTHORS

In accordance with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (URM), 1997

Our readers represent all branches of medicine. We wish to receive and publish manuscripts that are reliable and lively and that will improve the care of patients, the health of the public, or policies affecting either. Manuscripts should be of interest to a broad range of scholars, busy practitioners, students, and physicians in training who have a clinical orientation. The purpose of a paper or letter may be to report, inform, alert, review, and discuss, but, above all, to teach. Titles should be short and intriguing. Avoid the overuse of jargon, adverbs, and expendable words and phrases; use only standard abbreviations and acronyms; and use inclusive language (see AMA Manual of Style, 8th Edition). We appreciate your interest in The Western Journal of Medicine and our profession.

Manuscript Information

Manuscripts should be sent to the Editor, Linda Hawes Clever, MD, c/o Publisher, The Western Journal of Medicine, 1224 West Main Street, Suite 200, Charlottesville, VA 22903-2858. Manuscripts must be original, not previously published, and not under consideration by another publisher. If preliminary data were included in another presentation or publication, this should be noted in the cover letter, and a copy of that publication should be included. Any conflict of interest, actual or potential, should be revealed to the Editors (see Letter of Transmittal). Obtaining informed consent to protect patients' rights to privacy should be documented according to URM 1997.

All manuscripts should be double-spaced and, including references and abstract but not tables, should not exceed:

- Articles: 3,000 words (15 double-spaced pages)
- Conferences and Reviews: 3,000 words
- Topics in Primary Care Medicine: 3,000 words
- Case Reports, Alerts, and Notices: 1,500 words
- Commentaries: 2,000 words
- Lessons From the Practice: 1,000 words
- Letters to the Editor: 500 words
- Epitomes: 800 words

Manuscripts, except for Case Reports, Epitomes, and Lessons From the Practice, should include a nonstructured abstract of no more than 150–200 words summarizing the article. Abstracts should include a description of the purpose, design, patients, results, and conclusions.

Letters to the Editor must be double-spaced and will be published at the discretion of the Editors. They may be edited for style and brevity. Those of a scientific nature may be subject to peer review. They should be no more than 500 words in length. Authors will be sent page proofs before publication.

All manuscripts will be subject to peer review in addition to review by the Editors to determine the originality, validity, and importance of content and conclusions. Reviewers' comments will be returned with rejected manuscripts at the discretion of the Editors. All reviewers will remain anonymous but will be required to state possible conflicts of interest.

All accepted manuscripts are subject to copyediting, and the corresponding author is sent edited page proofs for approval and necessary minor changes. Excessive changes at this stage may result in a delay of publication or withdrawal of the paper. No changes will be made after the final, edited version has been approved by the corresponding author without notifying the author. It is the corresponding author's responsibility to clear all corrections and changes with coauthors.

Letter of Transmittal

All authors must sign the letter of transmittal, with one author designated as correspondent and his or her name, address, and telephone and fax numbers included.

The order of authorship is determined by the authors. All authors should meet the basic criteria for authorship (as stated below). Because the order of authorship is assigned in different ways, its meaning cannot be inferred accurately unless it is stated by the authors. Authors may explain the order of authorship in a footnote.

A letter of transmittal, except for one accompanying a manuscript from US Government employees whose work was done as part of their official duties, must include a paragraph that transfers copyright: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns, or otherwise conveys all copyright ownership to The Western Journal of Medicine, in the event that such work is published by the journal."

The letter of transmittal must include a statement of author responsibility signed by all authors: "I have participated in the conception and design of this work and in the writing of the manuscript and take public responsibility for it. I have reviewed the final version of the manuscript and approve it for publication. I attest to the validity and legitimacy of data in the manuscript and agree to be named as the lead author or coauthor of the manuscript."

The letter of transmittal must include a description of sources of funding and the role of sponsors, including their involvement, if any, in review and approval of the manuscript for publication. The letter must also include a statement of financial disclosure: "I warrant that I have no financial interest in the drugs, devices, or procedures described in the enclosed manuscript (except as disclosed in the attached statement)."

Research or project support should be included as a footnote to the manuscript or in the accompanying cover letter.

Manuscripts concerned with experimental investigation on human subjects must include in the text a statement that all subjects gave their informed consent and that approval was obtained from the appropriate ethics committee.

Acknowledgments will be printed on a select basis—to acknowledge those who contributed to but were not involved in the writing or review of the paper. They should not include persons whose work on the manuscript was a part of their regular duties.

Preparation of Manuscripts

Everything, including references, tables, figure legends, and abstracts, must be double-spaced.

Please submit the following: The original manuscript, two copies, and a copy of the manuscript on disk (labeled with the word processing program used). Allow a margin of 2.5 to 4 cm (1 to 1.5 in) on both sides. Be sure to include the references, tables, and figure legends on the disk. Formatting should be kept to a minimum. Manuscripts transmitted by facsimile machine are not acceptable unless requested by the Editors.

All values should be in Systeme International (SI) units, with metric equivalents following in parentheses. Tempera-ture readings should be given in Celsius. Use the generic name of drugs, with the salt or ester given at the initial mention of a drug.

Figures (illustrations) should be submitted in triplicate in black and white, unmounted 12.7 X 17.8 cm (5 X 7 in) glossy prints, with the figure number, lead author's name, and top of the photo indicated with a label on the back. Patients (and relatives) have a right to anonymity in published clinical documentation. Details that might identify patients should be avoided unless essential for scientific purposes. Masking of the eye region in photographs of patients may be inadequate protection of anonymity. If identification of patients is unavoidable, informed consent should be obtained. This should be clearly stated and proof submitted with the manuscript. Changing the data on patients should not be used as a way of securing anonymity.

Figure legends, to be typed in sequence on the same page, should be in complete sentences. Any figures or tables previously published must be accompanied by a letter of permission to borrow from the copyright holder (the previous publisher). The permission of the authors should also be obtained. The Editors discourage the use of borrowed figures or tables.

Reprints

A form for ordering reprints will be sent to the corresponding author when the article is published.

References

All references should be cited in the text using superscript numbers and listed in their order of citation. They should be pertinent to the text and not simply a listing of the results of a computerized search. They should be in URM style according to the following examples. Do not use op cit or ibid.

References should be medical, scientific, or scholarly publications. Others—such as newspapers or magazines—should be kept to a minimum.

Journal Articles

Abbreviations of journal titles should conform to those used in Index Medicus. List up to six authors; for seven or more, use et al after listing the first six.

1. Vega KJ, Pina I, Krevsky B. Heart transplantation is associated with an increased risk for pancreatobiliary disease. Ann Intern Med 1996; 124:980–983
2. Parkin DM, Clayton D, Black RJ, Masuyer E, Friedl HP, Ivanov E, et al. Childhood leukaemia in Europe after Chernobyl: 5 year follow-up. Br J Cancer 1996; 73:1006–1012

No author given:

3. Cancer in South Africa [editorial]. S Afr Med J 1994; 84(12):15

Books

4. Ringsven MK, Bond D. Gerontology and leadership skills for nurses. 2nd ed. Albany (NY): Delmar Publishers; 1996 [author of book is same as author of chapter]
5. Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press; 1995, pp 465–478 [authors of book differ from chapter author]

Correspondence

6. Shusterman D. Espresso maker's wrist [correspondence]. West J Med 1990; 152:721–722

Scientific or Technical Report

Issued by funding or sponsoring agency:

7. Smith P, Golladay K. Payment for durable medical equipment billed during skilled nursing facility stays. Final report. Dallas (TX): Dept of Health and Human Services (US), Office of Evaluation and Inspections; 1994 Oct. Report No.: HHSIGOEI69200860

Issued by performing agency:

8. Field MJ, Tranquada RE, Feasley JC, editors. Health services research: work force and educational issues. Washington DC: National Academy Press; 1995. Contract No.: AHCPR282942008. Sponsored by the Agency for Health Care Policy and Research
9. Centers for Disease Control and Prevention. Recommendations and Reports: 1997 Revised guidelines for performing CD4+ T-cell determinations in persons infected with human immunodeficiency virus (HIV) MMWR 1997; 46(Jan 10):RR-2

Proceedings

10. Kimura J, Shibasaki H, editors. Recent advances in clinical neurophysiology. Proceedings of the 10th

International Congress of EMG and Clinical Neurophysiology; 1995 Oct 15–19; Kyoto, Japan. Amsterdam: Elsevier; 1996

Mass Circulation Publications

11. Lee G. Hospitalizations tied to ozone pollution: study estimates 50,000 admissions annually. The Washington Post 1996 Jun 21; Sect A:3 (col 5)

Personal Communications and Unpublished Data

The use of "personal communication" or "unpublished data" should be avoided and should not be included in the reference list. If such a notation provides essential information not available from a public source, it should be given in parentheses in the body of the text, listing the person's name, highest academic degrees, and professional affiliation, whether the communication was oral or written, and the date (month and year):
12. Lyme disease has been reported in red squirrels (J. Sneed, PhD, Department of Wildlife, written communication, September 1990).

For Further Information

Questions regarding the Instructions for Authors may be directed to the Managing Editor, Allison Spearman, 1224 W. Main St., Ste. 200, Charlottesville, VA 22903-2858. Telephone (804) 817-2000, Fax (804) 817-2020.

Additional copies of Instructions for Authors are also available through an on-demand fax request line 24 hours a day. Call (804) 817-2000 to receive a faxed copy of the Instructions for Authors.

AUTHOR CHECKLIST

- ✓ Original manuscript and 2 copies; diskette.
- ✓ Everything double-spaced.
- ✓ Illustrations, black and white glossy, identified with lead author's name—3 sets, plus figure legends that describe fully and in complete sentences what the figure depicts.
- ✓ Letter of transmittal that includes release of copyright, statement of conflict of interest, funding source(s), and authorship responsibility, signed by all the authors.
- ✓ A 200-word unstructured abstract.
- ✓ Title page that includes current affiliation of all authors and an address and telephone and fax number for corresponding author.
- ✓ Permission-to-borrow letters for any previously published illustrations or tables.
- ✓ All references numbered consecutively, double-spaced, in URM style, and cited in text. No unpublished data or nonscientific publications listed in references (include in text).
- ✓ Informed consent obtained.

Classified Advertisements

The rate for each insertion is **$1.50 per word, with a 30 word ($45) minimum.** Confidential box number charge: $10 each month.
A word is defined as one or more letters bounded by spaces. The following gives some examples:

Linda H. Clever, MD	= 4 words
Send CV	= 2 words
A	= 1 word
February 22, 1997	= 3 words
allergy/immunology	= 1 word
Sacramento, CA 95817	= 3 words
804-979-8034	= 1 word

Classified display rate $70 per inch. Maximum sizes: 1 column by 5" or 2 columns by 2" (2-1/8" per column). Larger classified ad space by special arrangements.
Copy for classified advertisements should be received not later than **first of the month preceding issue. All copy must be typed or printed.** Classified advertisers using Box Numbers forbid the disclosure of their identity; your inquiries in writing will be forwarded to Box Number advertisers. Although *The Western Journal of Medicine* believes the classified advertisements in these columns to be from reputable sources, we do not investigate the offers made and assume no liability concerning them. The right is reserved to reject, withdraw, or modify all classified advertising copy in conformity with the decisions of the Advertising Committee.

Please Type or Print Advertising Copy

Classified Advertisements Are Payable in Advance
CLASSIFIED ADVERTISEMENTS, THE WESTERN JOURNAL OF MEDICINE
2 WEST TAUNTON AVENUE, BERLIN, NJ 08009
(609) 768-9360; FAX (609) 753-0064
Ads may be placed online at www.wjmed.com

PHYSICIANS WANTED

FAMILY PRACTICE

OREGON/SOUTHWEST WASHINGTON

Northwest Permanente, P.C., a stable, physician-managed multispecialty group of over 550 physicians providing quality care to 430,000 members of Kaiser Permanente in Oregon and Southwest Washington, has excellent opportunities for board certified or eligible family physicians. Our medical offices in Portland, Oregon have an outpatient clinical position that includes some urgent care; and our group in Longview has one position that requires OB skills.

Our program offers a professionally stimulating practice in one of the most successful managed care systems in the country. We also offer a competitive salary (signing bonus for Longview), and a full benefits package including a generous retirement program, professional liability coverage, sabbatical leave and more. To receive additional information, please forward inquiry and CV to: W.J. Clark, Director of Professional Resources, Northwest Permanente, P.C., 500 NE Multnomah, Suite 100, Portland, OR 97232-2099. (800) 813-3763. EOE.

KAISER PERMANENTE
Northwest Permanente, P.C.
Physicians and Surgeons

PHYSICIANS WANTED

WESTERN STATES OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 100 positions of various specialties. Both permanent and locum tenens. Send CV to:

Western States Physician Services
7510 No. Trellis Circle, Fresno, CA 93720
Call (800) 873-0786; FAX (800) 705-7943
email: weserve@lightspeed.net

CALIFORNIA

Int-rim PHYSICIANS

LOCUM TENENS
PERMANENT PLACEMENTS

Jim Ellis (800) 437-7676

Since 1979
the

Int-rim PHYSICIANS

LOCUM TENENS NETWORK has been taking the hassles of the paperwork and overhead out of practicing medicine. Practice near home or travel the country. We will coordinate all your travel details and provide you with the best occurrence malpractice policy available. Explore a partnership with Interim Physicians and open new horizons for your future.

Call today! (800) 333-7828

PHYSICIANS WANTED

OREGON AND THE NORTHWEST. Urban, suburban, rural locations; variety of practice arrangements; all specialties. Placement professionals for 20 yrs. Oberto & Associates, 920 Pinecrest Terr, Ashland, OR 97520. (800) 482-6656; FAX (541) 482-4951. No J-1 Opp. boberto@jeffnet.org.

PHYSICIAN - OUTPATIENT CLINIC - The County of San Mateo, located in the San Francisco Bay Area, has an immediate opening for a board certified/eligible physician for our Outpatient Clinic. A background in Family Practice or Internal Medicine. Spanish/English bilingual a plus. Full-time position with excellent benefits package. Fax resume to Dr. M. Pedersen at (650) 366-4732, or mail to 2710 Middlefield Road, Redwood City, CA 94063. EOE.

NATIONWIDE TRAVEL - Health research organization seeks physician for National Health & Nutrition Examination Survey sponsored by U.S. Public Health Service. Individual will be part of a large medical team conducting health exams in government mobile exam centers for a six-year data collection period. Work to begin February/March 1999. Must be licensed in one state. One year minimum commitment and FULL-TIME CONTINUOUS TRAVEL REQUIRED. Competitive salary, paid malpractice, per diem, car, 3-4 weeks paid vacation per year, holidays, and health, life, disability insurance offered. Call Beverly Geline, 800/937-8284 or e-mail: GELINEB1@Westat.com. Westat, Rockville, Maryland. EOE.

IDAHO

Make One Of America's Best Places to Live Even Better.

Where You'll Work.
Primary Health, Idaho's largest, fastest-growing integrated health care system whose network of family medicine immediate care centers, by-appointment family practitioners, pediatricians and OB/GYNs serves beautiful southern Idaho.

Where You'll Live.
In a great place to raise a family with quality schools, incredible outdoor recreation and a rural atmosphere close to a metropolitan area with a beautiful performing arts center, excellent hospitals and professional sports.

What You'll Get.
The financial backing and medical resources of a major health care network. A competitive salary, ownership options, flexible work and call schedules, professional growth, full benefits including medical and dental and much more

Submit CV and questions to:
BECKY NELSON
(800) 688-5008 ext 507 • FAX (208) 344-4262
Physician Recruitment
800 Park Boulevard, Suite 760
Boise, Idaho 83712

TEXAS TECH MEDICAL CENTER IN AMARILLO IS EXPANDING ITS FACULTY

We are seeking board certified, patient care oriented physicians who possess a strong desire and ability to teach. We encourage participation in clinical research. Physician/Faculty opportunities currently exist for the following specialists: **Family Physicians, General Internists, Obstetricians, Perinatologists and Psychiatrists.**

Texas Tech Medical Center in Amarillo is one of four campuses of the Texas Tech University Health Sciences Center and is comprised of medical, allied health and pharmacy school operations. The medical school campus has departments of Pediatrics, Family Medicine, Internal Medicine, Obstetrics/Gynecology, Psychiatry and Surgery. Residency programs are available in the four primary care departments.

The city of Amarillo is a thriving community of approximately 200,000 people located in the Texas Panhandle with unusually pleasant weather, a strong economic base, a low cost of living, a major medical community with two major hospitals and a veteran's hospital, very good public education including a major junior college and four-year universities in both Canyon and Lubbock, Texas as well as active arts programs. Located on Interstate 40, Amarillo is within an easy drive of the Dallas/Ft.Worth Metroplex, Denver, Santa Fe, Oklahoma City and numerous ski resorts. Please visit our web site at *http://www.ama.ttuhsc.edu/AMAHome.html* for more information.

The medical school in Amarillo offers competitive salaries and benefits. Inquiries from women and minorities are encouraged. To submit your curriculum vitae or if you have inquiries, please contact either:

E. Lee Taylor, M.D., Regional Dean
1400 Wallace Boulevard
Amarillo, Texas 79106
(806) 354-5401
e-mail <lee@cortex.ama.ttuhsc.edu>

Terry Myers, M.D., Ph.D., Associate Dean for Clinical Affairs
1400 Wallace Boulevard
Amarillo, Texas 79106
(806) 354-5413
e-mail <tmyers@cortex.ama.ttuhsc.edu>

Teaching. Caring. Healing.

ADVERTISING INDEX

Southern Medical Association . . .2nd Cover

MEDICINE + PSYCHIATRY . . . . . .3rd Cover

THE QUEST FOR MERCY . . . . . .4th Cover

UNIVERSITY OF COLORADO . . . . . .page 138

The Western Journal of Medicine

◀ Reprints ▶

Any article printed in *WJM* can be purchased in quantities of 100 or more. Printed on fine quality journal stock. Prices are based upon article length and quantity ordered.

Call Allison Spearman for prices and information, 8:30 – 5:30 EST, Mon– Fri, (804) 979-8034 ext. 146; or E-Mail to: aspearman@cjp.com

The Western Journal of Medicine

Practical Information for Practicing Physicians

Subscribe Now!

The Western Journal of Medicine extends its thanks to the loyal CMA members who have already made their commitment by subscribing to *WJM*. Here is your opportunity to support the revitalized *Journal*...**now available through subscription only**.

Your subscription to *WJM* features:

EPITOMES
Highlights of major advances in a different specialty each month with brief epitomes by experts in the field.

BIOMEDICAL SCIENCE
Five clinical research societies coordinate important new research findings, emphasizing clinical value.

SOCIOECONOMICS
WJM is often the first to predict, examine, and evaluate socioeconomic changes and trends.

CONFERENCES
All you need to know about medical conferences, nationally and locally.

The future of *WJM* is brighter than ever. Subscribe now so you won't miss a single monthly issue. Only $45 per year for affiliated association members ($65 for regular subscribers).

There are four easy ways to subscribe...

1 ***Call (804) 817-2000*** or

2 ***Fax this ad to (804) 817-2020*** or

3 ***Sign up online at www.wjmed.com*** or

4 ***Mail this ad to the address below***

...and there are three easy ways to pay:

Charge my: ☐ Visa ☐ MasterCard ☐ Check enclosed ☐ Bill me

Name on card _____

Card # _____ Exp. Date _____

Signature _____

Name _____

Address _____

City, State, Zip _____

Phone _____

Fax _____ E-Mail _____

The Western Journal of Medicine

Check One (12 issues):

☐ $45 Member Rate

☐ $65 Regular Rate

☐ $20 Student/Resident/Intern

☐ $90 Institutional Rate

Return to: *The Western Journal of Medicine*, 1224 West Main Street, Suite 200, Charlottesville, VA 22903-2858. Phone (804) 817-2000. Fax (804) 817-2020.

Changing Your Address?

If you are moving and/or would like your Journal sent to a new address...

1. Print your old mailing address below or attach an old mailing label below:

Name _____

Old Address _____

City _____

State _____

Zip _____

Telephone _____

2. Print or type your new mailing address:

Name _____

New Address _____

City _____

State _____

Zip _____

Telephone _____

Fax _____

E-Mail _____

3. Clip and mail this form to:

The Western Journal of Medicine
1224 West Main Street, Suite 200
Charlottesville, VA 22903-2858

4. Or, visit our web-site at:

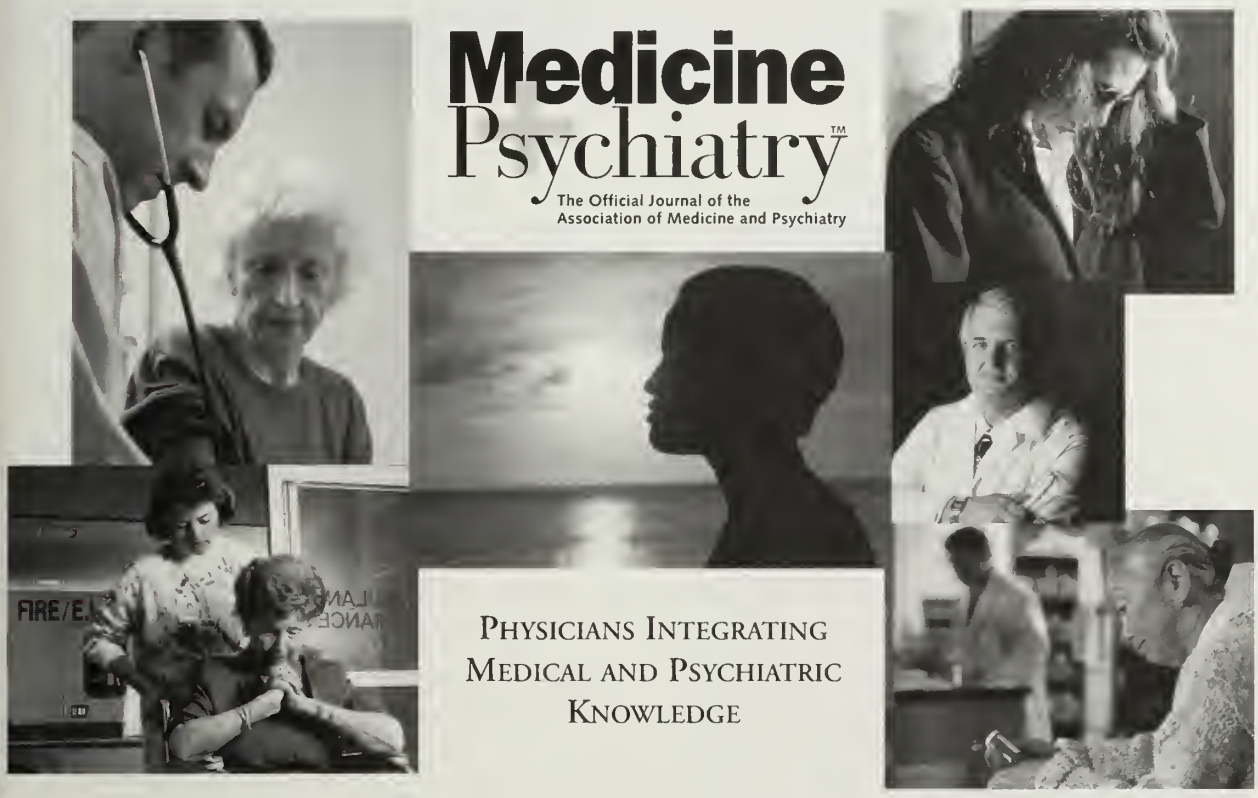
http://www.wjmed.com

The Western Journal of Medicine

www.wjmed.com

Practical Information for Practicing Physicians

Charter Subscription Rate!



- Original articles, reviews and case reports
- Clinical case conferences from Massachusetts General Hospital
- Content originating from the psychiatric problems that present in the primary care setting, emergency room, medical/psychiatric unit, geriatric unit, and consultation service

Charge my: ❑ Visa ❑ MasterCard ❑ Check enclosed ❑ Bill me

Card #_____

Exp. Date _____

Signature _____

Name _____

Institution/Title _____

Medical Specialty _____

Percentage of professional time spent: ___%Clinical ___%Research

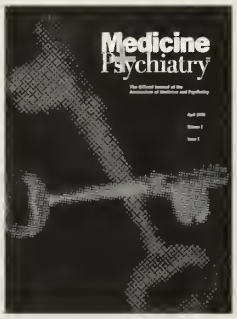
___%Teaching ___%Admin. ___%Other _____

Address _____

City, State, Zip _____

Phone _____

Fax _____



Check One (4 issues)

- ❑ $100 Individual Charter Rate
- ❑ $200 Institutional Rate
- ❑ $75 In-Training Rate
- ❑ $250 Outside North America

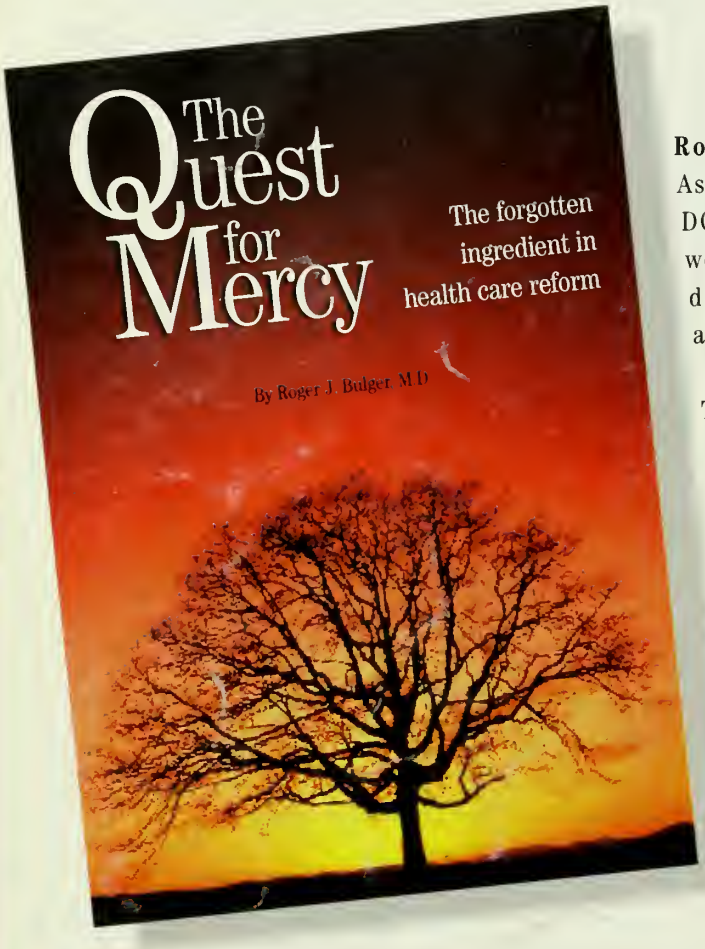
MP98

Return to: Medicine + Psychiatry, 1224 West Main Street, Suite 200
Charlottesville, VA 22903-2858 Phone (804) 979-4913 Fax (804) 979-4025

The Quest for Mercy

The forgotten ingredient in health care reform

by Roger J. Bulger, MD, FACP



Roger J. Bulger, MD, FACP is President of the Association of Academic Health Centers in Washington, DC. He has published scores of papers and chapters, as well as three books on subjects ranging from infectious diseases to medical education, humanities, Hippocrates, and, of course, academic health centers.

The Quest for Mercy is aimed at physicians, including young physicians and medical students. The book addresses managed care and managed cost, sickness and healing, hope and despair, relationships, oaths, populations, prevention, and patients.

"This book will become a classic."

Linda Hawes Clever, MD
Editor, THE WESTERN JOURNAL OF MEDICINE

The Complete Manuscript As Published In
The Western Journal of Medicine

ORDER YOUR COPIES NOW!

Per Copy: $10.00*

*Note: USA/Canada postage and handling included, all other countries please add US $6.00 Air Printed Matter postage. Please add Virginia and local sales tax where applicable. Quantity discounts available; please call.

I would like to order_____copy(ies) of **The Quest For Mercy**.

Payment must accompany order. Total amount enclosed $_____

NAME _____

INSTITUTION _____

ADDRESS _____

CITY/STATE/ZIP _____

COUNTRY _____

❑ Check Enclosed $_____ *please charge my* ❑ VISA ❑ MASTERCARD
(*make payable to:* The Western Journal of Medicine)

Account #_____ Exp. date _____

Signature _____

CARDEN JENNINGS PUBLISHING CO., LTD.

MAIL TO: *The Western Journal of Medicine*, 1224 West Main Street, Suite 200, Charlottesville, Virginia 22903-2858
Phone: (804) 979-8034 • Fax: (804) 979-4025 • www.wjmed.com

OFFICIAL JOURNAL OF

KA MEDICAL ASSOCIATION · ARIZONA MEDICAL ASSOCIATION · CALIFORNIA MEDICAL ASSOCIATION · DENVER MEDICAL SOCIETY · IDAHO MEDICAL ASSOCIATION · NEVADA STATE MEDICAL ASSOCIATION · NEW MEXICO MEDICAL SOCIETY · UTAH MEDICAL ASSOCIATION · WASHINGTON STATE MEDICAL ASSOCIATION · WYOMING MEDICAL SOCIETY

FRANCIS A. COUNTWAY
LIBRARY OF MEDICINE
BOSTON, MA
OCT 16 1998

The Western Journal of Medicine

VOLUME 169 • NUMBER 4 OCTOBER 1998

DISPLAY SHELVES

ARTICLES

201 Reducing Need and Demand for Medical Services in High-risk Persons—A Health Education Approach
J F FRIES and D MCSHANE

206 Drug-Resistant Pulmonary Tuberculosis in the Baja California-San Diego County Border Population
CR PETER, E SCHULTZ, K MOSER, M COX, R FREEMAN, M RAMIREZ-ZETINA, and M RODRIGUEZ LOMELI

CONFERENCES AND REVIEWS

214 Health and Safety Risks in Production Agricultural Workers
SG VON ESSEN and S MCCURDY

EPITOMES

221 Important Advances in Dermatology

ALERTS, NOTICES, AND CASE REPORTS

230 A Novel Approach to Understanding a Mysterious Murmur in a Young Adult After Surgical Repair of Tetralogy of Fallot
JB KINNEY, JR, VB HO, KM MIZELLE, and DJ SAHN

232 Case Presentation and Review: Constrictive Pericarditis
L OSTERBERG, R VAGELOS, and JE ATWOOD

TOPICS IN PRIMARY CARE MEDICINE

240 Low-Molecular-Weight Heparin in the Treatment of Deep Venous Thrombosis
KE HAUER

245 Primary Care for Those With Severe and Persistent Mental Illness
C CREWS, H BATAL, T ELASY, E CASPER, and PS MEHLER

COMMENTARY

251 A Cry From Within
KA DYER

EDITORIAL

253 A Great Opportunity
LH CLEVER

CORRESPONDENCE

254 Letter to the Editor
CP THEUER and H ANTON-CULVER

OTHER FEATURES

196 Continuing Medical Education Activities
255 Classified Advertising

Detailed Table of Contents: 194, 195

Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Medical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology

SMA – Your CME Resource

Southern Medical Association

92nd Annual Scientific Assembly

November 18-22, 1998
New Orleans, Louisiana
Ernest N. Morial Convention Center

Guest Speakers

These speakers were confirmed at press time. More will be confirmed later.

Allergy & Immunology
Ernest N. Charlesworth, M.D., Brenham, Tex.
I. Celine Hanson, M.D., Houston, Tex.

Cardiology
Bruce Lindsay, M.D., St. Louis, Mo.

Colon & Rectal Surgery
John Pemberton, M.D., Rochester, Minn.
George Fuhrman, M.D., New Orleans, La.

Dermatology
Vincent A. DeLeo, M.D., New York, N.Y.
Stephen E. Wolverton, M.D., Indianapolis, Ind.

Emergency Medicine
Larry Mellick, M.D., Augusta, Ga.
Rick Dart, M.D., Denver, Colo.

Family Practice
Martin Sullivan, M.D., Durham, N.C.
Frank Svec, M.D., Ph.D., New Orleans, La.

Gastroenterology
Charles Sninsky, M.D., Gainesville, Fla.
Eugene R. Schiff, M.D., Miami, Fla.

Geriatric Medicine
Charles A. Cefalu, M.D., New Orleans, La.
Laura Chiodo, M.D., San Antonio, Tex.

Gynecology
G. Rodney Meeks, M.D., Jackson, Miss.

Medical Management & Administration
Robert L. Marier, M.D., New Orleans, La.
Jane M. Orient, M.D., Tucson, Ariz.

Medicine
Dick Briggs, Jr., M.D., Birmingham, Ala.
Blase Carabello, M.D., Charleston, S.C.

Neurology & Psychiatry
Christopher C. Colenda, M.D., East Lansing, Mich.
Salvador Ceniceros, M.D., Johnson City, Tenn.

Neurosurgery
Peter J. Jannetta, M.D., Pittsburgh, Penn.
John D. Jackson, M.D., New Orleans, La.

Occupational & Environmental Medicine
Edward J. Doyle, Jr., M.D., M.S.C., Morgantown, W. Va.
John Walden, M.D., Huntington, W. Va.

Oncology
Kent Wallner, M.D., Seattle, Wash.
Susan Miesfeldt, M.D., Charlottesville, Va.

Ophthalmology
Kurt A. Buzard, M.D., F.A.C.S., Las Vegas, Nev.

Orthopaedic & Trauma Surgery
Gerald Engh, M.D., Arlington, Va.

Otolaryngology - Head & Neck Surgery
C. Blake Simpson, M.D., San Antonio, Tex.
Thomas B. Aufdemorte, D.D.S., San Antonio, Tex.

Pathology
John W. Bishop, M.D., Omaha, Neb.
Charles B. Root, M.D., West Dundee, Ill.

Pediatrics & Adolescent Medicine
Russell W. Steele, M.D., New Orleans, La.
Franklin G. Boineau III, M.D., New Orleans, La.

Plastic & Reconstructive Surgery
James Grotting, M.D., F.A.C.S., Birmingham, Ala.
John J. Coleman III, M.D., Indianapolis, Ind.

Radiology
Christopher R. B. Merritt, M.D., New Orleans, La.
Eva Rubin, M.D. Birmingham, Ala.

Rheumatology
Fred Wolfe, M.D., Wichita, Kan.
Virginia Steen, M.D., Washington, D.C.

Surgery
Edward L. Bradley III, M.D., Buffalo, N.Y.
J. David Richardson, M.D., Louisville, Ky.

Urology
Jonathan P. Jarow, M.D., Baltimore, Md.

CME Opportunities

- Twenty-eight Specialty Section meetings and a number of joint meetings
- Scientific and Clinical Symposia - "early bird" symposia with free breakfast and mid-day symposia with free lunch
- Case-driven Grand Rounds - Controversial Diagnoses 1998: Prostate Cancer; Domestic Violence; Incontinence; Neck Pain; Occupational Medicine and the Primary Care Physician
- "Dessert with the Experts" with Specialty Section guest speakers
- Special 2-hour "New Drugs Update" Symposium - part of SMA's Section Officers' Recognition Luncheon
- Managed Care Track on important nonclinical issues - contracting, capitation, forming physician organizations, improving practice efficiency, reimbursement and compliance
- Women's Health Track to focus on issues in women's health
- The President's Symposium - "Physician Leadership for the Next Century"

Special Events

Enhance your CME experiences with special events.

Opening Ceremony
Thursday, November 19, 8:30 - 10:00 AM
The keynote address by SMA President J. Lorin Mason, M.D., marks the official start of the 92nd Annual Scientific Assembly. Entertainment and introduction of other SMA leaders will round out the program. This program is free to registered participants.

Section Social Functions, New Member Reception, and Alumni Reunions
Thursday, November 19, times vary

Prayer Breakfast
Friday, November 20, 7:00 - 8:00 AM
Initiated last year, this popular event offers an environment of fellowship and worship. This program is free to registered participants.

President's Reception
Friday, November 20, 7:30 PM
Let the good times roll at the annual President's Reception, featuring a masked ball (costume optional) at Mardi Gras World. Tickets are $35/Adult and $15/Child 12 or younger.

President's-Doctor's Day Awards Luncheon
Saturday, November 21, 12:30 - 2:30 PM
Nationally known columnist and entertaining food critic Calvin Trillin will be the featured speaker. Tickets are $30 each.

President's Night Dinner Dance
Saturday, November 21, 6:30 - 11:30 PM
Great food and the heritage of Southern music wil highlight the President's Night Dinner Dance. And th Pink Flamingos are back to add their special brand o entertainment. Tickets are $85/Adult and $35/Chil 12 or younger.

For more information, call 800-423-4992

And more!!

- Insurance & Retirement Programs
- Exhibit Hall Activities
- Recreational Activities (Golf & Tennis Toumaments, Fun Run/Walk)
- Enrichment Programs
- Programs for Active Retired Members
- Over 30 hours of CME Credit offered for only $195.00 for SMA Members, $295 for Joining Members, and $445 for Nonmembers, and free for Medical Student, Residents and Fellows

The Southern Medical Association is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

92nd Annual Scientific Assembly
November 18-22 • New Orleans, Louisiana

THE FRANCIS A. COUNTWAY LIBRARY OF MEDICINE BOSTON, MA
OCT 16 1998

The Western Journal of Medicine®

SINCE 1902

1224 WEST MAIN STREET, SUITE 200 • CHARLOTTESVILLE, VIRGINIA 22903-2858
TELEPHONE (804) 817-2000; FACSIMILE (804) 817-2020; E.MAIL wjm@cjp.com

LINDA HAWES CLEVER, MD, *Editor*
EDWARD D HARRIS JR, MD, *Associate Editor*

ALLISON SPEARMAN, *Managing Editor*
DAVID ERN, *Marketing Director*

editorial communications to DR CLEVER • business communications to MS SPEARMAN

Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Medical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

SPECIAL EDITORS

Special Editor for Arizona
Marshall 8. 8lock, Phoenix, Ariz

Special Editor for Denver
David Shander, Denver, Colo

Special Editor for Idaho
E. R. W. Fox, Coeur d'Alene, Idaho

Special Editor for Nevada
Anton P. Sohn, Reno, Nev

Special Editor for New Mexico
I. 8rian Taylor, Carlsbad, NM

Special Editor for Utah
C. 8asil Williams, Salt Lake City, Utah

Special Editor for Washington
David Hopkins, Federal Way, Wash

Special Editor for Wyoming
Joseph P. Murphy, Casper, Wyo

ASSISTANT EDITORS

Clinical Investigation
H. 8enfer Kaltreider

Health and Public Policy
Ralph Crawshaw

International Health
Anvar Velji

Lessons From the Practice
Stephen J. McPhee
Jonathan E. Rodnick

Medical Staff Conferences
Nathan M. 8ass

Poetry
Margaret Kaufman

Primary Care Medicine
Stephen J. McPhee
Terrie Mendelson

Radiologic Cases
Jonathan M. Levy

EDITORIAL BOARD

Editor Emeritus
Malcolm S. M. Watts, San Francisco, Calif

Anesthesiology
Carol Lake, Sacramento, Calif

Biostatistics and Epidemiology
Virginia L. Ernster, San Francisco, Calif

Cardiac and Thoracic Surgery
Norman E. Shumway, Stanford, Calif

Dermatology
Clifton R. White Jr, Portland, Ore

Emergency Medicine
William A. 8oehm, Alamogordo, NM

General and Family Practice
Norman Kahn, Kansas City, Mo
Thomas E. Norris, Seattle, Wash
Joe Schoeber, Casper, Wyo

Internal Medicine
Albert Deisseroth, Houston, Texas
Alan Fogleman, Los Angelas, Calif
Patricia Gabow, Denver, Colo
John H. Holbrook, Salt Lake City, Utah
Philip Hopewell, San Francisco, Calif
Irwin J. Schatz, Honolulu, Hawaii
Walter E. Stamm, Seattle, Wash
Reginald Strickland, Albuquerque, NM
Stephen I. Wasserman, San Diego, Calif

Neurology
Robert Collins, Los Angeles, Calif
John Greenlee, Salt Lake City, Utah
Leslie Wiener, Los Angeles, Calif
Earl Zimmerman, Portland, Ore

Neurosurgery
George A. Ojemann, Seattle, Wash
Robert F. Spetzler, Phoenix, Ariz

Nuclear Medicine
Jerold M. Lowenstein, San Francisco, Calif

Obstetrics and Gynecology
Daniel Mishell Jr, Los Angeles, Calif

Occupational Medicine
Linda Rosenstock, Washington, DC

Ophthalmology
Sandy Feldman, La Jolla, Calif

Orthopedics
Thomas DeCoster, Albuquerque, NM

Pathology
Ronald Weinstein, Tuczon, Ariz

Pediatrics
Allen W. Mathies Jr, Pasadena, Calif
Diane Wara, San Francisco, Calif

Pharmacology
Rubin 8ressler, Tucson, Ariz

Physical Medicine and Rehabilitation
Julie G. Madorsky, Pomona, Calif

Preventive Medicine and Public Health
Joseph L. Lyon, Salt Lake City, Utah

Psychiatry
J. Christian Gillin, San Diego, Calif
Lewis Judd, La Jolla, Calif

Radiology
Gary Glazer, Stanford, Calif
Michael L. Manco-Johnson, Denver, Colo
Albert A. Moss, Seattle, Wash

Surgery
Haile T. Debas, San Francisco, Calif
Alex G. Little, Las Vegas, Nev

Urology
Linda Shortliffe, Stanford, Calif

Senior Members at Large
Thomas Elmendorf, Davis, Calif
Edgar Wayburn, San Francisco, Calif

ADVISORY BOARD, CLINICAL INVESTIGATION

Brian A. Cason, San Francisco, Calif
John Christenson, Salt Lake City, Utah
Kari Connolly, San Francisco, Calif
Bruce W. Goldberg, Portland, Ore
Philip Goodman, Reno, Nev
Roy Jones, Albuquerque, NM
Howard Lien, Tucson, Ariz
8arbara M. Lippe, Los Angeles, Calif
Michael W. McDermott, San Francisco, Calif
Jeanette Mladenovic, Denver, Colo
Kenneth M. Moser, San Diego, Calif
James C. Orcutt, Seattle, Wash
John Owings, Sacramento, Calif
Robert Robbins, Stanford, Calif
Henry Rosen, Seattle, Wash
Mary H. Samuels, Portland, Ore
George A. Sarosi, San Jose, Calif
Jeffrey Saver, Los Angeles, Calif
David Schriger, Los Angeles, Calif
Jack H. Simon, Denver, Colo
Peggy Sue Weintrub, San Francisco, Calif
Owen M. Wolkowitz, San Francisco, Calif

DISPLAY & CLASSIFIED ADVERTISING INFORMATION

CONTACT: MJ Mrvica Associates, Inc, 2 West Taunton Ave, 8erlin, NJ 08009 • (609) 768-9360/FAX (609) 753-0064
Advertisements—The journal is published the second week of the month. Display advertising must be received no later than the first of the month preceding issue.
Advertising rates will be sent on request. Acceptance of advertising is contingent upon approval by the Publisher.
The journal reserves the right to reject any advertisement.

SUBSCRIPTION INFORMATION

The subscription price per year is $65 in the United States and Canada (US funds); $80 in all other countries. Institutional rate $90. Single copies are $10. Special issues are $10. Address all subscription communications to:
THE WESTERN JOURNAL OF MEDICINE Circulation, 1224 W Main St, Suite 200, Charlottesville, VA 22903-2858 • Tel: (804) 817-2000

Allow six weeks for subscriptions to begin. Past issues must be bought individually. So long as reserve stocks are available, missing issue requests from subscribers are honored for up to six months after the issue date. Thereafter, the single copy rate of $10 is applicable for each issue available. Special issues are $10.

Chonge of Address—Requests for change of address should give both the old and new address. Allow six weeks for changeover.

SUBMITTING MANUSCRIPTS

Manuscripts for consideration should be sent to the managing editor, Allison Spearman, 1224 W Main St, Suite 200, Charlottesville, VA 22903-2858.

"Instructions for Authors"—A complete guide to manuscript submission and *WJM* style available from the publisher. Manuscripts may be prepared in accordance with the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals."

PUBLISHER

Copyright © 1998 by the British Medical Journal Publishing Group • Owned and Published by the British Medical Journal Publishing Group
All material subject to this copyright appearing in THE WESTERN JOURNAL OF MEDICINE may be photocopied for the noncommercial purpose of scientific or educational advancement.
Volumes begin with January and July.
THE WESTERN JOURNAL OF MEDICINE (ISSN 0093-0415/USPS 084 480) is published monthly by Carden Jennings Publishing Co, Ltd, 1224 W Main St, Charlottesville, VA 22903-2858. Periodicals postage paid at Easton, Pennsylvania.
POSTMASTER: Send address changes to *The Western Journal of Medicine*, Circulation, 1224 W Main St, Suite 200, Charlottesville, VA 22903-2858.

The Western Journal of Medicine

VOLUME 169 • NUMBER 4 • OCTOBER 1998

CONTENTS

ARTICLES

201 **Reducing Need and Demand for Medical Services in High-risk Persons—A Health Education Approach**

JAMES F. FRIES, MD, *and* DENNIS Mc SHANE, MD

From the Department of Medicine, Stanford University School of Medicine Stanford and Stanford University Medical Center, Palo Alto, California.

208 **Drug-Resistant Pulmonary Tuberculosis in the Baja California-San Diego County Border Population**

CHRISTOPHER R. PETER, PhD, ERIC SCHULTZ, MPH, KATHLEEN MOSER, MD, MPH, MILLICENT COX, PhD, ROBERT FREEMAN, MA, MARTHA RAMIREZ-ZETINA, MD, MPH, and MOISES RODRIGUEZ LOMELI, MD

From the Public Health Laboratory and Tuberculosis Clinic, San Diego County Health and Human Services Agency, and San Diego Dialogue, San Diego, California; Instituto Mexicano Seguro Social, Tijuana; Servicios Coordinados de Salud Pública de Baja California, Mexicali, Mexico.

CONFERENCES AND REVIEWS

214 **Health and Safety Risks in Production Agriculture**

SUSANNA G. VON ESSEN, MD, and STEPHEN McCURDY, MD

From the Department of Internal Medicine, Pulmonary and Critical Care Section, University of Nebraska Medical Center, Omaha; and the Department of Epidemiology and Preventive Medicine, University of California–Davis.

EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

Dermatology

Items of progress in dermatology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, as to both scientific fact and important clinical significance.

221 **Psoriasis Therapy Update**

BRUCE H. THIERS, MD

222 **The Pathogenesis of Kaposi's Sarcoma**

SARAH RODMAN, MS IV, and CLAY J. COCKERELL, MD

223 **Dermatoses of Pregnancy**

LISA M. COHEN, MD

224 **Evaluation and Treatment of Onychomycosis**

RICHARD K. SCHER, MD

225 **Public Awareness of the Threat of Melanoma and Performance of Skin Self-Examination**

JUNE K. ROBINSON, MD

225 **HIV Related Skin Diseases Clear with Combination Therapy**

MARCUS A. CONANT, MD

226 **The Role of Clostridium Botulinum: A Neurotoxin in Clinical Dermatology**

SETH L. MATARASSO, MD

226 **Disorders of Pigmentation: Global Issues of Major Cosmetic Concern**

PEARL E. GRIMES, MD

227 **Patient-Applied Treatment for External Genital Warts: The Time has Come**
KARL R. BEUTNER, MD, PhD

228 **Lasers for Removing Unwanted Hair and Rejuvenating Skin**
RONALD G. WHEELAND, MD

ALERTS, NOTICES, AND CASE REPORTS

230 **A Novel Approach to Understanding a Mysterious Murmur in a Young Adult After Surgical Repair of Tetralogy of Fallot**
COL JAMES B. KINNEY, JR, MC, USA; VINCENT B. HO, MD; CPT KATHERINE M. MIZELLE, MC, USAR; and DAVID J. SAHN, MD
From the Departments of Pediatrics and Radiology, Madigan Army Medical, Center, Tacoma, Washington, the Department of Radiology, Uniformed Services University of the Health Sciences, Bethesda, Maryland, and the Clinical Care Center for Congenital Heart Disease, Oregon Health Science University, Portland, Oregon.

232 **Case Presentation and Review: Constrictive Pericarditis**
LARS OSTERBERG, MD; RANDALL VAGELOS, MD; and J. EDWIN ATWOOD, MD
From the Stanford University School of Medicine, Palo Alto, California.

TOPICS IN PRIMARY CARE MEDICINE

240 **Low-Molecular-Weight Heparin in the Treatment of Deep Venous Thrombosis**
KAREN E. HAUER, MD
From the Division of General Internal Medicine, School of Medicine, University of California, San Francisco.

245 **Primary Care for Those With Severe and Persistent Mental Illness**
CYNTHIA CREWS, MD, HOLLY BATAL, MD, TOM ELASY, MD, EDMUND CASPER, MD, and PHILIP S. MEHLER, MD
From the University of Colorado Health Sciences Center and the Division of General Internal Medicine and Psychiatric Services at Denver Health Medical Center, Denver, Colorado.

COMMENTARY

251 **A Cry From Within**
KIRSTI A. DYER, MD, MS
From the Journey of Hearts: A Healing Place in Cyberspace.™

EDITORIAL

253 **A Great Opportunity**
LINDA HAWES CLEVER, MD

CORRESPONDENCE

254 **Letter to the Editor**
CHARLES P. THEUER, MD, and HODA ANTON-CULVER, PhD
Department of Surgery, University of California, Irvine Medical Center, Orange, California; and Division of Epidemiology, Department of Medicine, University of California, Irvine, California

OTHER FEATURES

196 **Continuing Medical Education Activities**
255 **Classified Advertising**

★ Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

Continuing Medical Education

ARIZONA • CALIFORNIA, HAWAII, NEVADA • COLORADO • IDAHO • NEW MEXICO • UTAH • WASHINGTON • WYOMING

ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

CARDIOLOGY

February 7–11, 1999—**International Congress XII on Endovascular Interventions.** Contact: Erika Scott (602) 266-2200 or fax (602) 265-8885. www.endovascularcongress.org

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (520) 626-7832; (800) 328-5868.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Paulette Richardson, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-3387. For more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

November 6–8—**10th Annual Anesthesiology Update: 1998.** UC Davis at La Monterey Plaza Hotel. Fri-Sun. 13 hrs. $350. Contact: UC Davis Office of Continuing Medical Education, 2315 Stockton Blvd, Camellia Cottage, Rm. 1019, Sacramento, CA 95817 (916) 734-5390

ALLERGY/IMMUNOLOGY

November—**Influenza Pandemic Preparedness.** Center for Disease Control at various sites around state. Thurs. 2.5 hrs. Call California Distance Learning Health Networks for satellite sites and fees (619) 594-3348.

CARDIOLOGY

October 31—**Update in Electrocardiography and Arrythmias.** UCSF at Radisson Miyako Hotel, San Francisco. Sat. 7.5 hrs. $195. Contact: UCSF (415) 476-5208.

January 7–10, 1999—**NewEra Cardiac Care:Innovation and Technology.** Marriott's Mountain Shadows Resort, Scottsdale Arizona. Sponsored by the Cardiothoracic Research &Education Forum. Contact:Aligned Management Associates, Inc. P.O. Box 23220, San Diego CA 92193 (760) 751-8841. Fax (760) 751-8842. www.amainc.com

January 18–22, 1999—**The 30th Annual Cardiovascular Conference at Snowmass.** Sponsored by the American College of Cardiology. To be held at Snowmass Conference Center, Snowmass, CO. 23 CME credits. Contact: Registration Secretary, Extramural Programs Dept., American College of Cardiology, 9111 Old Georgetown Rd., Bethesda, MD 20814-1699. Phone (800) 253-4636, ext.695 or Fax (301) 897-9745.

January 29–31, 1999—**Clinical Nuclear Cardiology:Case Review With the Experts. Cardiology Update 1998.** American College of Cardiology at San Francisco. Thurs.–Sat. Contact: ACC Extramural Programs (800) 253-4636.

February 18–20, 1999—**19th Annual Pathophysiology & Techniques of Cardiopulmonary Bypass.** San Diego Marriott Hotel & Marina. Sponsored by the Cardiothoracic Research &Education Forum. Contact:Aligned Management Associates, Inc. P.O. Box 23220, San Diego CA 92193 (619) 541-1444 or fax (619) 541-1447 www.amainc.com

DERMATOLOGY

January 14–17, 1999—**Practical Dermatology for the Primary Care Physician, San Diego, CA.** Sponsored by Continuing Medical Education Associates. To be held at the Hyatt Regency, La Jolla, San Diego, CA. Method: AV, L, SB, W. Thurs–Sun. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

March 4–7, 1999—**Practical Dermatology for the Primary Care Physician, Orlando, FL.** Sponsored by Continuing Medical Education Associates. To be held at the Buena Vista Palace at Walt Disney World Village, Orlando, FL. Method: AV, L, SB, W. Thus–Sun. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

May 23–26, 1999—**Practical Dermatology for the Primary Care Physician, Las Vegas, NV.** Sponsored by Continuing Medical Education Associates. To be held at the Caesars Palace, Las Vegas, NV. Method: AV, L, SB, W. Sun–Wed. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

EMERGENCY MEDICINE

October 19–20—**Trauma Uncensored: 1998.** UC Davis at Hyatt Regency, Sacramento. Mon.–Tue. 17 hrs. $250. Contact: (916) 734-5390.

October 19–23—**Emergency Medicine Symposium I.** UCSD at La Jolla Marriott, San Diego. Mon.–Fri. 32 hrs. $495. Contact: OCME (619) 534-3940.

October 26–30—**27th Annual Topics in Emergency Medicine.** UCSF at Radisson Miyako Hotel, San Francisco. Mon.–Fri. 32 hrs. $675. Contact: UCSF (415) 476-5208.

November 9–13—**Emergency Symposium III.** UCSD at La Jolla Marriott, San Diego. Mon.–Fri. 32 hrs. Contact: OCME (619) 534-3940.

December 4–5—**Trauma Care – Then and Now.** UCSF at Hotel Nikko, San Francisco. Fri.-Sat.. 12 hrs. $395-$450. Contact: UCSF (415) 476-5808.

December 14-18— **Emergency Symposium II.** UCSD at La Jolla Marriott, San Diego. Mon.–Fri. 32 hrs. Contact: OCME (619) 534-3940.

May 13-16, 1999—**Outdoor Emergency Medicine, Scottsdale, AZ.** Sponsored by Continuing Medical Education Associates. To be held at the Mariott Camelback Inn, Scottsdale, AZ. Method: AV, L, SB, W. Thurs–Sun. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

May 13-16, 1999—**Outdoor Emergency Medicine, Scottsdale, AZ.** Sponsored by Continuing Medical Education Associates. To be held at the Mariott Camelback Inn, Scottsdale, AZ. Method: AV, L, SB, W. Thurs–Sun. 32 hrs credit:AMA, AOA, AAFP. $750. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

ENDOCRINOLOGY

March 11–13, 1999—**The Fourth International Conference on Continuous Renal Replacement Therapies.** Hotel del Coronado in San Diego, California. Contact:Shirley Kolkey, Complete Conference Management, 1660 Hotel Circle North, #220, San Diego, CA 92108. (619) 299-6673 or fax (619) 299-6675.

ETHICS

October 22–34—**Seventh Annual Symposium on the Design and Methods of Clinical Trials.** UCSF at San Francisco. Thurs–Fri Contact:UCSF Office of Continuing Medical Education. (415) 476-4251.

FAMILY PRACTICE/PRIMARY CARE

October 22–26—**Masters of Medicine.** Sponsored by Continuing Medical Education Associates. Marriott Marquis, New York, NY. Thurs.–Mon. 30 hrs. Credit: AMA, AOA, AAFP. $795. Contact: Victoria Gonzales, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

October 30—**Breast-feeding, Ensuring Survival of Our Species.** Children's Hospital ans health Center at Escondido. Fri. 6.25 hrs. $50. Contact: San Diego County Breast-feeding Coalition, Nancy Wright (619) 576-5981.

November 14—**Women's Health Symposium.** UC Davis at UCD Med Ctr. Cancer Center Auditorium, Sacramento. Sat. Contact: UCD (916) 734-5390.

December 3–4—**Controversies in Women's Health.** UCSF at Cathedral Hill Hotel, San Francisco. Thurs.–Fri. 13 hrs. Credit. $370. Contact: UCSF (415) 476-5208.

January 14–17, 1999—**Practical Dermatology for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Regency, SF. Thurs.–Sun. 20 hrs. $575. Contact: Victoria Gonzales, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

January 14–17, 1999—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Regency, SF. Thurs.–Sun. 20 hrs. $575. Contact: Victoria Gonzales, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

February 11–14, 1999—**Office Gynecology and Women's Health for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Islandia, San Diego. Thurs.–Sun. 20 hrs. $575. Contact: Victoria Gonzales, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

February 12–14, 1999—**California Academy of Family Physicians (CAFP) 51 st Annual Scientific Assembly.** San Diego Concourse, San Diego, CA. 40 hrs. Contact: Clark Franklin, CAFP, 114 Sansome Street, Suite 1305, San Francisco, CA 94104-3824. (415) 394-9121 or fax (415) 394-9119.

February 17 –19, 1999—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF at Cathedral Hill Hotel, SF. Wed.–Fri. 16 hrs. $400. Contact:UCSF Program Coordinator, Dept. of Family and Community Medicine (415) 476-5250.

May 14–18, 1999—**Primary Care Essentials, San Francisco, CA.** Sponsored by Continuing Medical Education Associates. To be held at the Grand Hyatt on Union Square, San Francisco, CA. Method: AV, L, SB, W. Thurs–Sun. 32 hrs credit:AMA, AOA, AAFP. $750. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

GERIATRICS

November 8–11—**Geriatrics Update 1998.** Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego, CA. Sun.–Wed. 20 hrs. Credit: AMA, AOA, AAFP. $525. Contact: Victoria Gonzales, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

KEY TO ABBREVIATIONS

DREW:	Charles R. Drew Postgraduate Medical School, Office of Continuing Medical Education, (213) 563-4800.
LLU:	Loma Linda University, Continuing Medical Education Programs, (909) 824-4963.
STAN:	Stanford University, Postgraduate Education, (415) 723-5594.
UCD:	University of California, Davis, Office of Continuing Medical Education, (916) 734-5390.
UCI:	University of California, Irvine, Memorial/UCI Center for Health Education, (714) 824-5926.
UCLA:	University of California, Los Angeles, Continuing Education in Medicine and Health Sciences, (310) 794-2620.
UCSD:	University of California, San Diego, Office of Continuing Medical Education, (619) 534-3940.
UCSF:	University of California, San Francisco, Extended Programs in Medical Education, (415) 476-4251.
USC:	University of Southern California, Postgraduate Division, (800) USC-1119.

INFECTIOUS DISEASE

October 29–30—**Globally Emerging Viral Infections.** UCSF at Crowne Plaza Hotel-Union Square, SF. Thurs-Fri. 12 hrs. $415-$470. Contact: UCSF (415) 476-5808.

November 5–8—**Advances in Infectious Disease.** Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego, CA. Thurs.–Sun. 20 hrs. Credit: AMA, AOA, AAFP. $525. Contact: Victoria Gonzales, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200; http://www.cmea.com

November 19—**Preparing for the Coming Influenza Pandemic Satellite Course.** California Distance Learning Health Network at various sites throughout California. Thurs. 2.5 hrs. Fee varies. Contact:CDLHN (619) 594-3348.

December 2–6—**Internal Medicine- 1998 Fall Program.** Sponsored by Continuing Medical Education Associates. Boca Raton Resort and Club, Boca Raton, FL. Wed.–Tues. 30 hrs. Credit: AMA, AOA, AAP, AAFP. $750. Contact: Victoria Gonzales, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

December 3—**Surveillance of Vaccine-Preventable Diseases Satellite Course.** California Distance Learning Health Network at various sites throughout California. Thurs. 2.5 hrs. Fee varies. Contact:CDLHN (619) 594-3348.

December 9—**AIDS-Associated Malignancies: Biology and Clinical Management.** UCSF at Palace Hotel, San Francisco. Wed. Credit 4.5 hours. $135. Contact: UCSF (415) 476-5208.

December 10–12—**Clinical Care of the AIDS Pateient.** UCSF at Palace Hotel, San Francisco. Thurs-Sat. Credit 24 hours. $455. Contact: UCSF (415) 476-5208.

February 5–6, 1999—**Infectious Disease Update: 1999.** UC Davis at Hilton Hotel, Sacramento. Fri-Sat. Contact: UCD (916) 734-5390.

INTERNAL MEDICINE

March 19–25, 1999—**Internal Medicine, San Diego CA.** Sponsored by Continuing Medical Education Associates. To be held at the Hotel Coronado, San Diego, CA. Method: AV, L, SB, W. Fri–Thurs. 45 hrs credit:AMA, AOA, AAFP. $895. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

NEPHROLOGY

February 4–6, 1999—**Advanced Nephrology: Nephrology for the Consultant.** Sponsored by UC San Diego. To be held at the Coronado Island Marriott Resort, Coronado, CA. 17 hrs credit:AMA. $175, $425. Contact: Shirley Kolkey, 1660 Hotel Circle North, #220, San Diego, CA 92108. Phone (619) 299-6673 or Fax (619) 299-6675; email c-c-m@worldnet.att.net

OB/GYN

October 23–27—**OB/GYN Review.** Red Lion Hotel, Glendale. $675. Sat.–Tues. 38 hrs. Contact: USC School of Medicine, Postgraduate Division, 1975 Zonal Ave., KAM 307, Los Angeles, CA 90033-1039; Phone (213) 342-2555 or (800) USC-1119; Fax (213) 342-2152 or (888) 665-8650; email usccme@hsc.usc.edu.

December 6—**CTTR 105th Semi-Annual Cancer Seminar: Tumors of the Breast.** To be held at the Marriott at Coronado, San Diego. 8 hrs. $110, $265. Contact: California Tumor Tissue Registry; c/o LLU School of Medicine, 11021 Campus Ave., AH 335, Loma Linda, CA 92350. Phone (909) 824-4788 or Fax (909) 478-4188; email cttr@linkline.com.

February 11–14, 1999—**Office Gynecology and Women's Health for the Primary Care Physician, San Diego, CA.** Sponsored by Continuing Medical Education Associates. To be held at the Hyatt Islandia, San Diego, CA. Method: AV, L, SB, W. Thurs–Sun. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

February 25–28, 1999—**Office Gynecology and Women's Health for the Primary Care Physician, Orlando, FL.** Sponsored by Continuing Medical Education Associates. To be held at the Buena Vista Palace at Walt Disney World Village, Orlando, FL. Method: AV, L, SB, W. Thurs–Sun. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

OTOLOGY

November 5–7—**San Francisco Otology and Neurotology Update-1998.** UCSF at Ritz-Carlton Hotel San Francisco. Thurs-Sat. 19 hrs. $475. Contact:UCSF (415) 476-5808.

October 17–21—**1998-99 Temporal Bone Surgical Dissection Courses.** Also to be held December 5–9; January 16–20, 1999; February 6–10, 1999; March 13–17, 1999; April 17–21, 1999; May 15–19, 1999; June 26–30, 1999; September 11–15, 1999; October 16–20, 1999; November 6–10, 1999; December 4–8, 1999. $1100, $1300. Contact Antonio De la Cruz, MD, House Ear Institute, 2100 W. Third Street, Los Angeles, CA 90057. Phone (213) 483-4431 or Fax (213) 483-8789.

ORTHOPEDICS

January 14–17, 1999—**Office Orthopedics and Bone Radiology for the Primary Care Physician, San Diego, CA.** Sponsored by Continuing Medical Education Associates. To be held at the Hyatt Regency, La Jolla, San Diego, CA. Method: AV, L, SB, W. Thurs–Sun. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: CMEA Monica L. Lier. (800) 993-2632 or (619) 674-5200.

February 25–28, 1999—**Office Orthopedics and Bone Radiology for the Primary Care Physician, New Orleans, LA.** Sponsored by Continuing Medical Education Associates. To be held at the Royal Sonesta Hotel, New Orleans, LA. Method: AV, L, SB, W. Thurs–Sun. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

February 25–28, 1999—**Office Orthopedics and Bone Radiology for the Primary Care Physician, Las Vegas, NV.** Sponsored by Continuing Medical Education Associates. To be held at the Caesars Palace, Las Vegas, NV. Method: AV, L, SB, W. Sun–Wed. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

PATHOLOGY

December 6—**CTTR 106th Semi-Annual Cancer Seminar: Tumors of the Head and Neck.** To be held at the Westin South Coast Plaza, Costa Mesa. 8 hrs. $110, $265. Contact: California Tumor Tissue Registry; c/o LLU School of Medicine, 11021 Campus Ave., AH 335, Loma Linda, CA 92350. Phone (909) 824-4788 or Fax (909) 478-4188; email cttr@linkline.com.

PEDIATRICS

December 4–6—**Stabilization and Management of the Critically Ill Child.** UCSF at Grand Hyatt Hotel, SF. Fri-Sun. 12 hrs. $300. Contact: UCSF (415) 476-5808.

January 29–31,1999—**37TH Clinical Conference Pediatric Anesthesiology.** Disneyland Hotel, 1150 W. Cerritos Avenue, Anaheim, CA 92802. Sponsored by The Pediatric Anesthesiology Foudation. $250-$295. Contact David J Steward, M.B., Program Director, Pediatric Anesthesiology Conference Box #3, Childrens Hospital Los Angeles, P.O. Box 54700, Los Angeles, CA 90054. (213) 669-2262 or fax (213) 660-8983.

February 14–17, 1999—**Pediatrics Update 1999, San Diego, CA.** Sponsored by Continuing Medical Education Associates. To be held at the Hyatt Islandia, San Diego, CA. Method: AV, L, SB, W. Sun–Wed. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

February 28–March 3, 1999—**Pediatrics Update 1999, Orlando, FL.** Sponsored by Continuing Medical Education Associates. To be held at the Buena Vista Palace at Walt Disney World Village, Orlando, FL. Method: AV, L, SB, W. Sun–Wed. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

PSYCHIATRY

November 6–8—**44th Annual Group Therapy Symposium.** UCSF at UCSF. Fri–Sun. 20 hrs. $295-$340. Contact:UCSF (415) 476-5808.

RADIOLOGY

October 23–25—**18th Annual Comprehensive Review of Vascular and Interventional Radiology.** The Hotel Del Coronado, San Diego. Credit 19 hrs. AMA. $300-$500. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773 or fax (770)552-9859; email: webmaster@ryalsmeet.com. www.ryalsmeet.com

October 26–November 1—**23rd Annual San Diego Postgraduate Radiology Review Course.** The Hotel Del Coronado, San Diego. Credit 39 hrs. AMA. $700-$995. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773 or fax (770)552-9859; email: webmaster@ryalsmeet.com. www.ryalsmeet.com.

October 29–November 1—**2nd Annual Intensive Review of Neuro, Head, and Neck Radiology.** The Four Seasons Resort Hotel, Newport Beach, California. Credit 28 hrs. AMA. $450-$725. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773 or fax (770)552-9859; email: webmaster@ryalsmeet.com. www.ryalsmeet.com

October 30–November 1—**Breast Imaging and Interventions Update.** The Hotel Del Coronado, San Diego. Credit 15 hrs. AMA. $275-$450. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773 or fax (770)552-9859; email: webmaster@ryalsmeet.com. www.ryalsmeet.com

February 25–28, 1999—**Up to Date Radiology in the Desert.** Mira Monte Resort, Indian Wells, California. Credit 26 hrs. AMA. $495-$750. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

SURGERY

January 15–16, 1999—**What's New General Surgery.** UC Davis at Hyatt Regency Sacramento at Capitol Park. Fri-Sat. Contact: UCD (916) 734-7203.

GENERAL/MULTIDISCIPLINARY

October 22–23—**Seventh Symposium on Clinical Trials: Design, Methods, and Controversies.** UCSF Laurel Heights Campus, San Francisco. Contact: UCSF Office of Continuing Medical Education (415) 476-4251 or fax (415) 476-0318.

October 26–28—**Telemedicine IV.** UC Davis at Hilton Hotel, Anaheim. Mon.–Wed. Contact: (916) 734-5390.

November 6–7—**Palliative Care Workshop.** UC Davis at Hyatt Regency Sacramento. Thurs-Fri. $200. Contact: UCD (916) 734-7203.

May 16–19, 1999—**Alternative Medicine, Scottsdale, AZ.** Sponsored by Continuing Medical Education Associates. To be held at the Mariott Camelback Inn, Scottsdale, AZ. Method: AV, L, SB, W. Sun–Wed. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

LOSS PREVENTION

October 20—**A Quality Improvement Program to Protect Your Medical Practice.** Medical Insurance Exchange of California. at Holiday Inn Select, Fairfield. Tues 2 hrs. Free or $40 to non members. Contact: David Carp (800) 227-4527.

November 3—**Medical Records Documentation for Patient Safety and Physician Defensibility.** Medical Insurance Exchange of California. at Santa Fe Bar and Grill, Berkeley. Tues. Free or $40 to non members. Contact: David Carp (800) 227-4527.

November 10—**Preventing "Failure to Diagnose" Malpractice Claims.** Medical Insurance Exchange of California. at San Francisco Medical Society. Wed. Free or $40 to non members. Contact: David Carp (800) 227-4527.

November 11—**Medical Records Documentation for Patient Safety and Physician Defensibility.** Medical Insurance Exchange of California. at Embassy Suites Hotel, Walnut Creek. Wed. Free or $40 for non members. Contact: MIE (800) 227-4527.

LEARNING SPANISH

October 23–26 (Los Angeles); December 4–7 (San Diego); January 22–25 (Los Angeles)—**Conversation in Spanish.** Maricopa Health System. 36 hrs. $695. Contact: Rios Associates (520) 881-3295; (619) 218-4875; Fax (520) 325-4258.

HOME STUDY/SELF ASSESSMENT

California Physicians' Legal Handbook Series. California Medical Association. Contact: CMA, PO Box 7690, San Francisco 94120-7690. (800) 882-1262.

Breast Cancer, Early Detection and Control. Texas Medical Association. **CD ROM.** $70. 2 hrs. Contact: Texas Medical Association, (800) 880-1300; http://www.texmed.org/health_science/hs_poep.html

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Second Wednesday of Each Month—**Cardiovascular Education Series.** St Anthony Hospital at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

February 4–6, 1999—**Neurology For The Non-Neurologist.** Hyatt Regency, Cancun Mexico. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

February 5–7, 1999—**Arrhythmias: Interptretation, Diagnosis & Management** MGM Grand, Las Vegas, NV Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

February 12–14, 1999—**Clinical Endocrinology For Primary Care Physicans.** Beaver Run Resort, Breckenridge, CO.Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

February 19–21, 1999—**Managing Respiratory Diseases.** Marriot's Casa Marina,Key West,FL. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

February 25–27, 1999—**Dermatology For The Non-Dermatologist.** Atlantis Paradise Resort, Bahamas. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

February 26–28, 1999—**Coronary Heart Disease Update.** Hilton Tapatio Cliffs, Scottsdale, AZ. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

March 12–14, 1999—**Dermatology For The Non-Dermatologist.**Riviera Hotel & Casino, Las Vegas, NV. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

March 25–27, 1999—**Neurology For The Non-Neurologist.** Grand Beach Resort, St. Thomas, USVI. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

March 25–27, 1999—**Clinical Endocrinology For Primary Care Physicans.** Marriott's Beach Resort, St. Grand Cayman. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

March 26–28, 1999—**Managing Respiratory Diseases.** Buena Vista Palace,Orlando,FL. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 8–10, 1999—**Coronary Heart Disease Update.** Hyatt Regency, Aruba Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 8–10, 1999—**Clinical Endocrinology For Primary Care Physicans.** The Westin Resort, St John, USVI. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 9–11, 1999—**Arrhythmias: Interptretation, Diagnosis &Management** Hilton Tapatio Cliffs, Scottsdale, AZ. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 9–11, 1999—**Neurology For The Non-Neurologist.** Marriott's Casa Marina, Key West, FL. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 23–25,1999—**Managing Respiratory Diseases.** Bally's, Las Vegas, NV. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 23–25,1999—**Dermatology For The Non-Dermatologist.** Parc Fifty-five, San Francisco, CA. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 30–May 2, 1999—**Dermatology For The Non-Dermatologist.** South Sea Plantation, Captiva Island, FL. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 30–May 2, **Clinical Endocrinology For Primary Care Physicans.** Hyatt Regency, New Orleans, LA. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

May 14–16, 1999—**Managing Respiratory Diseases.** Hilton Resort, Hilton Head, SC. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

May 14–16, 1999—**Neurology For The Non-Neurologist.** Bally's, Las Vegas, NV. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

IDAHO

The listing of continuing medical education programs in Idaho is compiled by the Ada County Medical Society. To list CME programs here, please send information at least two months in advance to: Ada County Medical Society, Inc. 305 W. Jefferson, PO Box 2668, Boise, Idaho 83701. (208) 336-2930.

Brochures, course information, and registration forms are available from the contact person or organization.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

Every First and Third Tuesday—**Building and Implementing Clinical Practice Guidelines at the Point of Care.** Contact: Thomas A. Naegele, DO, (505) 275-7267.

SATELLITE COURSES

Contact: Joe Treat or Jim Cato, Immunization Program, (505) 827-2366

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

January 6–10, 1999—**MRI at Snowbird**. Cliff Lodge, Snowbird, Utah. Credit 20 hrs. AMA. $400-$650. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773 or fax (770)552-9859; email: webmaster@ryalsmeet.com. www.ryalsmeet.com

MEDICAL GRAND ROUNDS

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics.** Contact: UUSM.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Ave, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 S Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 340-2058.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Ste 1100, Seattle, WA 98121. (206) 441-9762.

OTHER CME OPPORTUNITIES

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

AMERICAN ASSOCIATION FOR THE STUDY OF HEADACHE. November 6–8, 1998—**Scottsdale Headache Symposium.** Scottsdale at Marriott's Camelback Inn Resort & Spa. Contact: (609) 845-1720.

Annual Meeting and Course: International Spine Imaging Symposium. February 15–17, 1999. Registry Resort, Naples, Florida. Credit 19.5 hrs. AMA. $250-$650. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

Breast Imaging Today and Tomorrow. November 2–5, 1998. The Ritz-Carlton Resort Hotel, Naples Florida. Credit 26 hrs. AMA. $650. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

Breast Imaging Today and Tomorrow. January 25–28, 1999. Boca Raton Resort and Club, Boca Raton, Florida. Credit 23 hrs. AMA. $495-$695. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

Breast Imaging Today and Tomorrow. February 15–19, 1999. Buena Vista Palace Resort and Spa, Lake Buena Vista, Florida. Credit 23 hrs. AMA. $495-$695. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

Conference on Patient Education. November 11–14, 1998. Hyatt Regency Austin, Austin, Texas. Contact: Ray Rosetta, Meetings and Programs Director, Society of Teachers of Family Medicine, 8880 Ward Parkway, Kansas City, Missouri 64114. Phone (800) 274-2237, ext. 4512.

Conference on Patient Education. November 19–22, 1998. Disney's Coronado Springs Resort, Orlando, Florida. Contact: Ray Rosetta, Meetings and Programs Director, Society of Teachers of Family Medicine, 8880 Ward Parkway, Kansas City, Missouri 64114. Phone (800) 274-2237, ext. 4512.

Musculoskeletal MR. October 22–25, 1998. The Westin Resort Hotel, Hilton Head, South Carolina. Credit 18 hrs. AMA. $650. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

Musculoskeletal MR. January 18–22, 1999. The Ritz-Carlton Resort Hotel, West Palm Beach, Florida. Credit 22.5 hrs. AMA. $450-$695. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

Predoctoral Education Conference. February 4–7, 1999. Savannah Marriott Riverfront, Savannah, Georgia. Contact: Ray Rosetta, Meetings and Programs Director, Society of Teachers of Family Medicine, 8880 Ward Parkway, Kansas City, Missouri 64114. Phone (800) 274-2237, ext. 4512.

STFM Family Conference. March 3–7, 1999. Kiawah Resort, Kiawah Island, South Carolina. Contact: Ray Rosetta, Meetings and Programs Director, Society of Teachers of Family Medicine, 8880 Ward Parkway, Kansas City, Missouri 64114. Phone (800) 274-2237, ext. 4512.

5th Annual Neuroradiology: A Comprehensive Review. February 2–6, 1999. The Ritz-Carlton Resort Hotel, West Palm Beach, Florida. Credit 24 hrs. AMA. $450-$695. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

32nd Annual Spring Conference. April 28–May 2, 1999. Sheraton Seattle Hotel & Towers, Seattle, Washington. Contact: Ray Rosetta, Meetings and Programs Director, Society of Teachers of Family Medicine, 8880 Ward Parkway, Kansas City, Missouri 64114. Phone (800) 274-2237, ext. 4512.

58th Annual American Occupational Health Conference. April 23–30, 1999. Ernest N. Morial Convention Center, New Orleans, Louisiana. Contact: ACOEM Education Dept., 55 W. Seeger Road, Arlington Heights, IL 60005; (847) 228-6850 or fax (847) 228-1856; www.acoem.org.

NOTICE

State Associations should send their CME listings for publication to:

Allison Spearman, Managing Editor
Western Journal of Medicine
1224 W Main St, Ste 200
Charlottesville, VA 22903-2858

(804) 979-8034 • Fax (804) 979-4025 • wjm@cjp.com

Articles

Reducing Need and Demand for Medical Services in High-risk Persons

A Health Education Approach

JAMES F. FRIES, MD, *and* DENNIS McSHANE, MD, *Palo Alto, California*

We undertook this study to identify persons with high medical use to target them for health promotion and self-management interventions specific to their problems. We compared the reductions in cost and health risk of a health education program aimed at high-risk persons with a similar program addressed to all risk levels. We compared health risk and use in 2,586 high-risk persons with those of employee (N = 50,576) and senior (N = 39,076) groups and contrasted results in specific high-risk disease or behavior categories (modules)—arthritis, back pain, high blood pressure, diabetes mellitus, heart disease, smoking, and obesity—against each other, using validated self-report measures, over a 6-month period. Interventions were a standard generic health education program and a similar program directed at high risk individuals (Healthtrac). Health risk scores improved by 11% in the overall high-risk group compared with 9% in the employee group and 6% in the senior group. Physician use decreased by 0.8 visits per 6 months in the high-risk group compared with 0.05 and 0.15 visits, respectively, per 6 months in the employee and senior groups. Hospital stays decreased by 0.2 days per 6 months in the high-risk group compared with 0.05 days in the comparison groups. The duration of illness or confinement to home decreased by 0.9 days per 6 months in the high-risk group and 0.15 and 0.25, respectively, in the employee and senior groups. Using imputed costs of $130 per physician visit, $1,000 per hospital day, and $200 per sick day, previous year costs were $1,138 in direct costs for the high-risk groups compared with $352 and $995 in the employee and senior groups, respectively. At 6 months, direct costs were reduced by $304 in the high-risk group compared with $57 and $70 in the comparison groups. Total costs were reduced $484 in the high-risk groups compared with $87 in the employee group and $120 in the senior group. The return on investment was about 6:1 in the high-risk group compared with 4:1 in the comparison groups. Effective health education programs can result in larger changes in use and costs in high-risk persons than in unscreened persons, justifying more intensive educational interventions in high-risk groups.

(Fries JF, McShane D. Reducing need and demand for medical services in high-risk persons: a health education approach. West J Med 1998; 169:201–207)

The ability of well-designed health education, health promotion, and self-management programs to improve health, reduce health risks, and decrease medical care costs has now been extensively documented.[1–17] Several reviews describe recent progress with the use of these programs.[18–20] Cost savings in the first year of effective programs appear to be due largely to an increased use of self-management techniques and increased personal self-efficacy. Subsequently, a reduction in illness burden due to the postponement or prevention of costly, chronic illness can lead to further cost savings.[1]

Theoretically, the effectiveness and cost savings of such programs might be greatest if they were targeted at persons at high risk of illness or who have high medical use. If these persons can be identified, more intensive interventions could be channeled toward the specific problems of persons who are in greatest need. The identification of groups of persons who will have substantially greater use in the following year than the average

From the Department of Medicine, Stanford University School of Medicine Stanford and Stanford University Medical Center, Palo Alto, California.
Reprint requests to James F. Fries, MD, Stanford University Medical Center, 1000 Welch Rd, Suite 203, Palo Alto, CA 94304-5755.

person has become possible.[20–22] On the other hand, persons with established chronic illness or with the worst health habits may not be as amenable to improvement through health education programs as those without these conditions or may be most intractable to making behavior changes. Few studies have been done that explore these issues.

The programs studied (Healthtrac, Inc., Menlo Park, California) have been documented to improve health habits, decrease health risks, and reduce costs in many randomized controlled and observational studies for as long as 30 months.[11–20] These studies have included the study of specific high-risk categories. Effectiveness and cost reduction has thus been documented by randomized trial in chronic disease programs such as those aimed at arthritis[15,17] and Parkinson's disease.[16]

In this study, we compare the results of programs directed at specific high-risk groups—including the arthritis program previously documented by randomized trial[15,17]—against each other and against comparison groups receiving the standard Healthtrac program, previously proved effective by randomized control trial. We compared effectiveness and cost savings in high-risk persons with standard Healthtrac programs directed at unscreened persons and also results in specific high-risk "modules"—programs targeted at arthritis, back pain, high blood pressure, combined risk, diabetes mellitus, heart problems, smoking, and weight loss—against each other.

Methods and Subjects

Methods

High-risk persons were identified by using the Healthtrac health assessment questionnaire with a multiple regression–based algorithm designed to predict medical care costs over the following 12 months based on age, sex, prior use, health risk score, smoking behavior, patients' self-reported health status, and the presence of chronic illness. The algorithm has been shown to predict both self-reported costs and claims costs over the following 12 months.[23]

The algorithm was developed by using a data bank of 24,626 subjects in the Healthtrac and Senior Healthtrac programs. Subjects were divided into learning and test data sets by random assignment. Univariate correlates between variables in the first study year and costs in the second year were examined in the learning data set. Stepwise multiple regression with the most promising variables was used to create a model for prediction and tested against the test data set. Predicted costs were compared with self-reported costs for the second year and with claims experience from Blue Shield of California, San Francisco. Claims costs in the highest decile were 12 times greater than claims costs in the lowest decile. Analysis of the program in high-risk subjects, performed by MEDSTAT Inc., Ann Arbor, Michigan, showed a return-on-investment quotient of 6.7:1 (R. Goetzel, M.D., R. Canto, J. Murnane: "A Return-on-Investment Analysis of the Citibank Health Management Program," unpublished manuscript).

Participants identified as high risk were allocated to a specific high-risk educational module by a second computer algorithm based on a ranking of the relative seriousness of particular chronic illnesses and health habits and the "most serious medical problem," as reported by the participant. Twelve such high-risk module programs were used: arthritis, back pain, high blood pressure, diabetes mellitus, heart problems, smoking, obesity, stroke, chronic obstructive pulmonary disease, alcohol intake, and a final group in which a combination of risks and disease factors established a risk for high use. We report the results of the entire high-risk group and of eight high-risk modules for which data on 100 or more participants were available.

Healthtrac programs use two-page health assessment questionnaires, either general health-oriented questionnaires or ones tailored to specific problem areas. Questionnaires have been repeatedly validated[12–14,24–27] and widely used. Participants receive a letter (signed by a physician) identifying their most problematic areas with specific recommendations for behavior change and self-management. Participants also receive a graphic summary of their individual health risk problems; subsequent progress; and books, audiotapes, and videotapes specific to these identified risks.[11–17] The program proceeds in cycles of six months in the standard programs and three months in the high-risk program modules. During each cycle, each participant receives a questionnaire, a letter, a report, and health education material. More than 40 separate sets of materials are used.

The programs are designed to increase self-efficacy (health confidence) and to effect specific behavioral changes. In addition, each module has specific goals. For example, the diabetes module is designed to improve risk factor profiles for cardiovascular disease, minimize complications, and reduce the frequency of hospital admissions for diabetic ketoacidosis and of leg ulcers and amputations by regular self-care.[28,29] Programs are not presented as "high risk" to the participant but as individually titled modules—that is, "Accent on Arthritis" or "Accent on Diabetes." The costs per participant are about $30 per year for the standard program and about $100 per year and $50 per six months for the high-risk programs.

A parallel study design was used in which the standard Healthtrac program is compared with the high-risk program, and individual high-risk modules are compared with each other. Data were gathered by a self-reported health assessment questionnaire at baseline and at six months. Many validation studies have been performed for these techniques.[11–16,24–27] Identical techniques and outcome measures were used for all groups. Primary dependent variables[30] were the overall health risk score, self-reported medical use (the number of physician visits and number of hospital days), and indirect costs as represented by "days sick or confined to home." Cost data are obtained for the previous six months and have been annualized in the tables for convenience in interpretation. The overall health risk score is computed from individual

TABLE 1.—*Baseline Characteristics of Participant Groups**

Variable	All High Risk	Comparison Employee	Comparison Senior	Arthritis	High Blood Back Pain	Combined Pressure	Diabetes Risk	Heart Mellitus	Cigarette Problems	Smoking	Weight Loss
No.	2,586	50,576	39,076	297	472	378	576	146	160	200	314
Age, yr	49.7	41.2	73.3	65.9	46.3	54.3	41.5	55.5	55.5	39.7	40.7
Blood pressure, mm of mercury											
Systolic	130	120	135	132	125	139	123	132	130	121	128
Diastolic	78	76	77	77	76	85	77	77	74	76	79
Cholesterol level, mmol/liter (mg/dl)	5.30 (205)	5.07 (196)	5.56 (215)	5.40 (209)	5.04 (195)	5.33 (206)	5.61 (217)	5.17 (200)	5.30 (205)	5.25 (203)	5.15 (199)
Kg (lb) over ideal weight	10.9 (24)	5.0 (11)	4.5 (10)	7.2 (16)	6.8 (15)	10.0 (22)	6.4 (14)	10.9 (24)	5.4 (12)	10.0 (22)	33.1 (73)
Body mass index	27	24	25	26.1	25.2	27.3	25.0	28.2	25.5	26.1	36.4
Seat-belt use, %	85	90	89	92	88	89	76	83	94	78	85
Fiber servings/day	2.5	2.8	3.2	3.0	2.5	2.6	1.9	3.1	3.1	1.8	2.5
Dietary fat, % calories	36	25	30	29	35	28	44	35	25	42	39
Saturated fat, % calories	14	13	11	11	13	11	15	14	9	16	15
Smokers, %	14	11	8	8	11	6	3	10	4.4	100	4.0
Packs/day	1.1	0.9	0.9	1.0	1.0	1.0	0.5	1.0	1.2	1.2	0.5
Alcohol, %	28	37	38	32	34	32	24	15	40	31	13
Oz/day	1.3	1.3	1.6	1.3	1.1	1.4	1.4	1.4	1.4	1.5	1.2
Exercise, %	82	86	83	91	88	89	71	84	85	81	78
Minutes/wk	120	174	159	144	136	135	64	122	159	122	114
Stress, %	34	30	6	18	33	26	51	22	15	41	40
Global health	41.2	27.6	29.8	39.9	36.9	36.6	40.1	44.2	45.3	44.4	47.1
Health risk score	23.5	18.2	17.4	18.1	18.8	19.7	25.1	21.8	16.3	42.5	26.8

*The data are given as the mean for each group.

health risks—smoking, saturated fat intake, lack of exercise—using algorithms based on the Framingham and other established risk factor models.[31–33] Cost imputations used charges of $130 for a physician visit (which includes the costs of the visit and associated laboratory tests, x-ray tests, and drugs), $1,000 per hospital day, and $200 per day sick or confined to home. The costs for physician visits and hospital days were estimated from claims data for similar groups of patients for 1994.[12–14]

Subjects

The study group comprised 2,586 consecutive subjects participating in the high-risk program and completing questionnaires at zero, three, and six months. Most of these subjects were members of employee groups, were principally white-collar workers, had private health insurance, and had a mean age of 49.7 years. We developed two large comparison groups as convenience samples. To approximate the age distribution, we selected an employee comparison group, aged a mean of 41.2 years, from consecutive participants enrolled in the standard Healthtrac program during the same time period—also principally white-collar workers, employed, and with private health insurance—who completed questionnaires at zero and six months. Similarly, a group of consecutive participants in the senior Healthtrac program, aged a mean of 73.3 years, was selected; senior status itself may be considered a high-risk characteristic.

Results

Characteristics of the participant groups are listed in Table 1. Specific high-risk patients have ages ranging from means of 65.9 years for patients with arthritis to about 40 years for patients with stroke or morbid obesity. The group with obesity weighed a mean of 33 kg (73 lb) above ideal, with a mean body mass index (weight [kg]/[height (meter)]^2) of 36.4. The blood pressure in the patients with hypertension was apparently well controlled with medication at study entry. The highest fat intake was seen in the combined-risk group and in patients reporting strokes. The highest saturated fat intake was reported in patients with stroke, those with obesity, and patients in the combined-risk group. Most persons reported at least some exercise; the combined-risk group, which includes the "worried well," had the lowest exercise levels. Stress scores were highest in the combined-risk and smoking groups.

Global health scores were drawn from a horizontal analogue scale that ranged from 0, indicating excellent health, to 100, indicating very poor health. Global health

TABLE 2.—*Baseline Costs*

Variable	*All High Risk*	*Comparison Employee*	*Comparison Senior*	*Arthritis*	*Back Pain*	*High Blood Pressure*	*Combined Risk*	*Diabetes Mellitus*	*Heart Problems*	*Cigarette Smoking*	*Weight Loss*
Physician visits/6 mo	3.75	1.55	2.65	4.1	4.4	2.7	3.35	4.1	4.45	3.75	4.0
Cost of physician visits, $, at $130	488	202	345	533	572	351	436	533	579	488	520
Hospital days/6 mo	0.65	0.15	0.65	0.60	0.45	0.40	0.45	1.40	2.10	0.5	0.55
Cost of hospital days, $, at $1,000	650	150	650	600	450	400	450	1,400	2,100	500	550
Sick days/6 mo	3.85	1.60	2.05	2.95	5.00	1.55	4.05	4.15	4.80	5.10	3.65
Cost of sick days, $, at $200	770	320	410	590	1,000	310	810	830	960	1,020	730
Direct costs, imputed, $	1,138	352	995	1,133	1,022	751	886	1,933	2,679	988	1,070
Total costs, imputed, $	1,908	672	1,405	1,723	2,022	1,061	1,696	2,763	3,639	2,008	1,800

scores were worse in the groups with obesity, heart problems, and diabetes mellitus and in smokers. Health risk scores were worst in the smoking group, in large part as a result of high scores in various categories beyond the smoking behavior itself.

Table 2 lists six-month medical use and imputed costs for the different groups at baseline. The high-risk group had previous six-month direct medical costs of $1,138 compared with $352 in the employee comparison group and $995 in the senior comparison group. Thus, the algorithms were effective in identifying high-risk persons. Total direct and indirect costs were $1,908 in the high-risk group, $672 in the employee comparison group, and $1,405 in the senior comparison group. Of individual modules, the highest previous six-month costs were in patients with heart problems, with a total of $3,639 in direct and indirect costs, followed by patients with diabetes mellitus at $2,763. Persons with back pain and cigarette smokers had the next highest total costs, at slightly more than $2,000 per six months for each. Absenteeism was greatest in smokers, followed by patients with heart problems and those with back pain. In contrast, smokers had relatively low direct costs in the previous six months.

Table 3 shows health risk and health risk component change scores at six months. For convenience in interpretation, scores have been reversed in Table 3 for seat-belt use, number of fiber servings per day, exercise percentage, and minutes of exercising per week so that in all cases a minus sign indicates improvement. Change scores are percentage changes from baseline, except for cigarette

TABLE 3.—*Health Risk Change Scores at 6 Months*

Variable	*All High Risk*	*Comparison Employee*	*Comparison Senior*	*Arthritis*	*Back Pain*	*High Blood Pressure*	*Combined Risk*	*Diabetes Mellitus*	*Heart Problems*	*Cigarette Smoking*	*Weight Loss*
No.	2,586	50,576	39,076	297	472	378	576	146	160	200	314
Cholesterol*,‡	+0.3	–0.5	–0.8	+0.2	+2.2	+0.6	–1.9	–0.2	–1.9	+1.9	+2.8
Body mass index	0.0	+0.1	–0.1	–0.1	0.0	–0.1	+0.2	0.0	0.0	+0.3	–0.3
Seat-belt use, %	–6.2	–2.3	–1.2	–2.6	–2.9	–5.5	–14.0	–5.3	–0.1	–5.1	–7.5
Fiber servings/day‡	–0.2	0.0	0.0	–0.2	–0.3	–0.2	–0.4	0.0	–0.2	–0.3	–0.2
Dietary fat, % calories	–9	–16	–13	–2	–6	–5	–17	–3	–12	–5	–7
Saturated fat, % calories	–6	–15	–14	+3	–2	–6	–14	+2	–7	–6	–3
Smoking, %	–6	–8	–9	–19	+6	+8	+2	+2	–14	–8	+1
Packs/day‡	–0.1	0.0	0.0	+0.1	0.0	–0.1	+0.1	+0.1	–0.2	0.0	+0.2
Alcohol intake, %	+1.4	–2.0	–4.0	+3.0	–3.0	+1.0	+4.0	+6.0	–14.0	0.0	+3.0
Oz/day	–0.1	0.0	–0.1	0.0	0.0	–0.1	–0.3	–0.3	–0.1	–0.3	+0.1
Exercise, %†	–6.0	–5.0	–1.0	–2.0	–0.7	–4.0	–23.0	–3.0	–4.0	+3.0	28
Minutes/wk †,‡	–25	–9	–5	–17	–17	–20	–47	–44	–24	–19	–18
Stress, %	–17	–26	0	–19	–3	–25	–25	–19	–24	–8	–12
Global health	–2.0	–2.5	–3.0	–7.5	–3.1	–6.3	+5.5	–6.1	–12.4	+2.3	+3.4
Health risk score	–11.0	–8.8	–5.7	–7.7	–7.8	–10.7	–17.9	–6.0	–9.2	–7.3	–7.8

*Percentage change score is based on cholesterol level in milligrams per deciliter, rather than millimolars per liter. †The sign has been reversed so that a negative value represents a favorable change for all variables. ‡Absolute change. Other values are percentage changes from baseline.

TABLE 4.—*Cost Changes per Participant at 6 Months*

Variable	*All High Risk*	*Comparison Employee*	*Comparison Senior*	*Arthritis*	*Back Pain*	*High Blood Pressure*	*Combined Risk*	*Diabetes Mellitus*	*Heart Problems*	*Cigarette Smoking*	*Weight Loss*
No.	2,586	50,576	39,076	297	472	378	576	146	160	200	314
Baseline	3.75	1.55	2.65	4.1	4.4	2.7	3.35	4.1	4.45	3.75	4.0
6 Months	2.95	1.5	2.5	3.45	3.45	2.35	2.35	3.8	3.35	2.65	2.9
Change	-0.8	-0.05	-0.15	-0.65	-0.95	-0.35	-1.0	-0.3	-1.1	-1.1	-1.1
Dollar Change	-104	-7	-20	-85	-124	-46	-130	-39	-143	-143	-143
Hospital Days											
Baseline	0.65	0.15	0.65	0.6	0.45	0.4	0.45	1.4	2.1	0.5	0.55
6 Months	0.45	0.1	0.6	0.45	0.35	0.15	0.35	1.4	0.6	0.75	0.15
Change	-0.2	-0.05	-0.05	-0.15	-.01	-0.25	-0.1	0.0	-1.5	+0.25	-0.4
Dollar Change	-200	-50	-50	-150	-100	-250	-100	0.0	-1500	+250	-400
Sick Days											
Baseline	3.85	1.6	2.05	2.95	5.00	1.55	4.05	4.15	4.8	5.1	3.65
6 Months	2.95	1.45	1.8	2.65	4.35	1.8	2.45	3.7	1.85	3.85	2.6
Change	-0.8	-0.15	-0.25	-0.3	-0.65	+0.25	-1.6	-0.45	-2.95	-1.25	-1.05
Dollar Change	-180	-30	-50	-60	-130	+50	-320	-90	-540	-250	-210
Direct Costs											
Baseline	1138	352	995	1133	21022	1751	886	1933	2679	988	1070
6 Months	834	295	925	899	799	456	656	1894	1036	1095	527
Change	-304	-57	-70	-235	-224	-296	-230	-39	-1643	+107	-543
% Change	-27	-16	-7	-21	-22	-39	-26	-2	-61	+11	-51
Total Costs											
Baseline	1906	672	1405	1723	2022	1061	1696	2763	3634	2008	1800
6 Months	1424	585	1285	1429	1664	816	1146	2634	1466	1865	1047
Change	-484	-87	-120	-295	-354	-246	-550	-129	-2233	-143	-753
% Change	-25	-13	-9	-17	-17	-23	-32	-5	-61	-7	-42

packs per day, ounces of alcohol per day, and exercise minutes per week where absolute changes are noted. Change scores for the cholesterol levels are based on conventional units, rather than Système International units.

Overall health risk scores improved by 11% over six months in the high-risk groups compared with 9% in the employee comparison group and about 6% in the senior comparison group, consistent with previous studies.[11–17] Although improvement was seen in most variables and in all specific modules, few changes were seen in reported cholesterol levels, body mass index, or dietary fiber intake.

Table 4 presents cost changes per participant at six months, showing baseline values, values at six months, the absolute change, and the imputed change in dollars. Direct costs are the sum of costs for physician visits and for hospital days. Total costs also include costs for sick days. Favorable changes were noted in nearly all categories and in essentially all modules.

Overall, the high-risk group had a reduction in imputed direct costs of $304 compared with $57 in the employee comparison group ($P < .01$) and $70 in the senior comparison group ($P < .01$). Percentage changes were also highest in the high-risk group, where an overall 27% reduction in direct costs was seen compared with 16% in the employee comparison group and 7% in the senior group. Total costs (including absenteeism or number of days confined to home) yielded cost savings of $484 in the high-risk group compared with $87 in the employee group and $120 in the senior group.

In the comparisons across individual high-risk groups, the numbers of subjects are smaller, and the results are more likely to be influenced by a few outliers. A single participant in the smoking group had 120 days of hospitalization and was excluded from the smoking subgroup computations but was included in the overall high-risk computations discussed earlier. Significance values have not been computed for these results because of the issue of multiple comparisons and the instability of hospital costs due to low sample sizes. Nevertheless, the consistency of results across groups is striking. The cigarette smoking group is the only one that did not show an overall direct cost decrease, due to a small increase in the hospital day category; however, reductions in physician visits, absenteeism, and total costs were seen in this group.

Change scores between the overall high-risk group and the comparison groups for the major comparisons of total direct costs and total costs were significantly different ($P < .01$) and were not significantly different between the two comparison groups. Differences in baseline and six-month values for health risk score, direct costs, and total costs were significant ($P < .01$) for all three groups using two-tailed t tests. Savings-to-cost ratios were approximately 4:1 for the standard programs and 6:1 for the high-risk programs.

Discussion

Health education programs directed at persons at high risk can be effective in changing behaviors and reducing use. Cost reductions can be greater in these targeted programs than in programs directed at unscreened populations, in part because the levels of use are greater, and a similar percentage reduction results in a larger decrease in use.

Several caveats apply. These programs were specifically designed to both change behaviors and reduce costs and included targeted objectives for each model; programs using different educational models or techniques might not have similar results. These programs were based on self-efficacy and readiness-to-change models. High-risk modules focus on targeted goals of both self-management and behavioral change. The intervention is tailored to each person's problems.

This study is not a randomized trial, and the usual caveats about observational studies apply. Dependent variables are obtained by self-report. The standard Healthtrac programs and specific high-risk modules, however, have been studied by randomized trials with essentially identical results, providing the support for this study.[11–17] These previous studies have included claims data analyses, again with congruent results. That any self-report bias would operate differently in the different participant groups being compared seems unlikely.

This study was for six months and raises the issue of the durability of the response over longer periods. A similar program without further reinforcement in arthritis by our group[5] showed continued effects after four years, suggesting that learned behaviors may be carried forward. With continued intervention, continued improvement has been noted for as long as 30 months.[11] The high-risk program, with continued intervention, remains highly effective after 32 months (R. Goetzel, R. Canto, J. Murhane: "A Return-on-Investment Analysis of the Citibank Health Management Program," unpublished manuscript). Thus, beneficial effects may be seen as early as six months and may increase over time.

The possibility of regression to the mean for the cost data must be considered because subjects were selected in part by their experiences in the previous six months. Opposite biases are also present because costs and use are expected to increase with increased age, and the costs of treating chronic illnesses are expected to rise slowly with the duration of the illness. Thus, any regression to the mean effects should be most important in the risk factor behavior modules (smoking, obesity, and combined risk) and least important in the chronic disease modules (arthritis, diabetes mellitus, hypertension, and heart problems). In contrast, results were generally less impressive in the behavioral modules than in the chronic disease modules. Moreover, this study was congruent with randomized controlled trials of these interventions showing effective behavioral change and cost reduction; such trials are not susceptible to regression to the mean effects.[12–17]

These results support the hypothesis that greater program benefits may accrue to health education programs targeted at high-risk populations. They do not, however, suggest that educational programs should be directed at only high-risk persons. Although baseline costs average three times as much in the 20% of a screened population at highest risk compared with the rest of that population, about half of the total costs reside with the other 80%. Furthermore, for programs based at the worksite or in a managed care population, singling out high-risk persons for intervention might increase concerns about lack of confidentiality or cause those not receiving an intervention to feel undervalued. An increase in the intensity of an intervention for those at high risk seems an appropriate strategy.

REFERENCES

1. Fries JF, Koop CE, Beadle CE, Cooper PP, England MJ, Greaves RJ, et al. Reducing health care costs by reducing the need and demand for medical services. N Engl J Med 1993; 329:321–325

2. Golaszewski T, Snow D, Lynch W, Yen L, Solomita D. A benefit-to-cost analysis of a work-site health promotion program. J Occup Med 1992; 34:1164–1172

3. Lorig K, Kraines RG, Brown BW Jr, Richardson N. A workplace health education program that reduces outpatient visits. Med Care 1985; 23:1044–1054

4. Vickery DM, Golaszewski TJ, Wright EC, Kalmer H. The effect of self care interventions on the use of medical service within a Medicare population. Med Care 1988; 26:580–588

5. Lorig KR, Mazonson PD, Holman HR. Evidence suggesting that health education for self-management in patients with chronic arthritis has sustained health benefits while reducing health care costs. Arthritis Rheum 1993; 36:439–446

6. Baum WB, Beracki EJ, Tsai SP. A preliminary investigation: effect of a corporate fitness program on absenteeism and health care cost. J Occup Med 1986; 28:18–22

7. Bertera RL. The effects of workplace health promotion on absenteeism and employee costs in a large industrial population. Am J Public Health 1990; 80:1101–1105

8. Blair SN, Smith M, Collingwood TR, Reynolds R, Prentice MC, Sterling CL. Health promotion for educators: impact on absenteeism. Prev Med 1986; 15:166–175

9. Bly J, Jones RC, Richardson JE. Impact of worksite health promotion on health care costs and utilization: evaluation of Johnson & Johnson's Live for Life program. JAMA 1986; 256:3235–3240

10. Vickery DM, Kalmer H, Lowry D, Constantine M, Wright E, Loren W. Effect of self-care education program on medical visits. JAMA 1983; 250:2952–2956

11. Fries JF, Fries ST, Parcell CL, Harrington H. Health risk changes with a low-cost individualized health promotion program: effects at up to 30 months. Am J Health Promot 1992; 6:364–371

12. Fries JF, Harrington H, Edwards R, Kent LA, Richardson N. Randomized controlled trial of cost reductions from a health education program: the California Public Employees' Retirement System (PERS) study. Am J Health Promot 1994; 8:216–223

13. Leigh JP, Richardson N, Beck R, Kerr C, Harrington H, Parcell CL, et al. Randomized controlled study of a retiree health promotion program: the Bank of America Study. Arch Intern Med 1992; 152:1201–1206

14. Fries JF, Bloch DA, Harrington H, Richardson N, Beck R. Two-year results of a randomized controlled trial of a health promotion program in a retiree population: the Bank of America Study. Am J Med 1993; 94:455–462

15. Gale FM, Kirk JC, Davis R. Patient education and self-management: randomized study of effects on health status of a mail-delivered program. Arthritis Rheum 1994;37:S197

16. Montgomery EB, Lieberman A, Singh G, Fries JF. Patient education and health promotion can be effective in Parkinson's disease: a randomized controlled trial. Am J Med 1994; 97:429–435

17. Fries JF, Carey C, McShane DJ. Patient education in arthritis: randomized controlled trial of a mail-delivered program. J Rheumatol 1997; 24:1378–1383

18. Pelletier K. A review and analysis of the health and cost-effective outcome studies of comprehensive health promotion and disease prevention programs. Am J Health Promot 1991; 5:311–315

19. Pelletier KR. A review and analysis of the health and cost-effective outcome studies of comprehensive health promotion and disease prevention programs at the worksite: 1991–1993 update. Am J Health Promot 1993; 8:50–62

20. Chapman L. Proof positive: analysis of the cost-effectiveness of worksite wellness. 3rd ed. Seattle (Wash): Summex Corp; 1991

21. Duan N, Manning WG, Morris CN, Newhouse JP. A comparison of alternative models for the demand for medical care. J Business Econ Stat 1983; 1:115–126

22. Van Vilet RCJA. Predictability of individual health care expenditures. J Risk Insur 1992; 59:443–465

23. Fries JF, Bailey L, Richardson N. Identification and intervention with high-risk individuals. Soc Prospective Med 1998; in press

24. Fries JF, Spitz PW, Young DY. The dimensions of health outcomes: the health assessment questionnaire, disability and pain scales. J Rheumatol 1982; 9:789–793

25. Fries JF. Toward an understanding of patient outcome measurement. Arthritis Rheum 1983; 26:697–704

26. Brown JF, Kazis LE, Spitz PW, Gertman P, Fries JF, Meenan RF. The dimensions of health outcomes: a cross-validated examination of health status measurement. Am J Public Health 1984; 9:161–180

27. Ramey DR, Raynauld JP, Fries JF. The health assessment questionnaire 1992: status and review. Arthritis Care Res 1992; 5:119–129

28. Anderson RM, Funnell MM, Butler PM, Arnold MS, Fitzgerald JT, Feste CC. Patient empowerment: results of a randomized controlled trial. Diabetes Care 1995; 18:943–949

29. Brown SA. Meta-analysis of diabetes patient education research: variations in intervention effects across studies. Res Nurs Health 1992; 15:409–419

30. Fries JF, Spitz PW. Quality of life studies: the hierarchy of patient outcomes. In: Spiker B, ed. Quality of life assessment for clinical trials. New York (NY): Raven Press; 1990

31. US Dept of Health and Human Services Task Force on Health Risk Assessment. Determining risks to health: federal policy and practice. Dover (Mass): Auburn House; 1986

32. Kannell WB, McGee D, Gordon T. A general cardiovascular risk profile: the Framingham study. Am J Cardiol 1976; 38:46–51

33. Multiple Risk Factor Intervention Trial Research Group. Multiple Risk Factor Intervention Trial (MRFIT): risk factor changes and mortality rates. JAMA 1982; 248:1465–1477

Articles

Drug-Resistant Pulmonary Tuberculosis in the Baja California-San Diego County Border Population

CHRISTOPHER R. PETER, PhD, ERIC SCHULTZ, MPH, KATHLEEN MOSER, MD, MPH, *and* MILLICENT COX, PhD, *San Diego, California*; ROBERT FREEMAN, MA, *El Centro, California*; MARTHA RAMIREZ-ZETINA, MD, MPH, *Tijuana, Baja California*; MOISES RODRIGUEZ LOMELI, MD, *Mexicali, Baja California*

A study was conducted to determine the frequency of, and risk factors for, drug-resistant pulmonary tuberculosis (TB) among Baja California (BC) and San Diego County (SDC) residents. Another purpose was to document the amount of contact between pulmonary TB patients and residents of the opposite side of the the border. During the period from February 1995 to May 1996, pulmonary TB patients from BC (n = 427) and SDC (n = 331) were evaluated with cultures, drug susceptibility tests, and questionnaires. Drug resistance was found in 41% of the BC Mycobacterium tuberculosis complex (MTB) isolates and 20% of the SDC isolates. Resistance to both isoniazid (INH) and rifampin (RIF) varied from 1% of isolates from SDC patients to 17% of isolates from BC patients. Patients with a history of previous treatment had increased odds of drug-resistant disease. Older BC patients were more likely to have INH- or RIF-resistant TB. Although 42% of Tijuana TB patients reported recent contact with residents from SDC, travel to Mexico and contact with residents from Mexico were not significant risk factors for drug-resistant TB among SDC residents. However, the demonstrated contact between TB patients and residents on opposite sides of the border indicates the importance of coordinating efforts internationally to control TB.

(Peter CR, Schultz E, Moser K, Cox M, Freeman R, Ramirez-Zetina M, Rodriguez Lomeli M: Drug-resistant pulmonary tuberculosis in the Baja California-San Diego county border population. West J Med 1998; 169:208-213)

Although the international boundary divides communities in Southern California and northern BC, these areas are closely linked geographically and economically. Each month there are an average of more than 5 million events of individuals crossing the border northbound between San Diego and Tijuana.[1] The number of individuals traveling southbound is approximately equal to the number traveling northbound.[1] Tuberculosis continues to pose a significant public health problem for communities on both sides of the border.[2] While comprehensive data are available on the incidence of drug-resistant disease among SDC patients through the county's Tuberculosis Control Program, there are only limited data available on drug-resistant TB among BC residents.[2] In addition, there is no published information available on the amount of contact that occurs between TB patients in BC and SDC with residents from the opposite sides of the border.

The purposes of this study were to

- Determine the proportion of drug-resistant disease among patients with pulmonary TB in BC and SDC border communities during a defined time period,
- Determine whether contact occurs between TB patients in BC and SDC and residents from the opposite sides of the border,
- Identify risk factors for drug-resistant TB among pulmonary TB patients in this population.

Patients and Methods

For purposes of this study, patients were classified as having "pulmonary TB" if they had a sputum culture positive for MTB, which includes *M. tuberculosis* and *M. bovis*.

From the Public Health Laboratory (Dr Peter and Mr Schultz) and Tuberculosis Clinic (Dr Moser), San Diego County Health and Human Services Agency, and San Diego Dialogue (Dr Cox), San Diego, California; Instituto Mexicano Seguro Social, Tijuana (Dr Ramirez); Servicios Coordinados de Salud Pública de Baja California, Mexicali (Dr Rodriguez), Mexico.

Preliminary results from this study were presented at the 37th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, Canada, September 1997 (abstract E-162). This project was approved by the Committee on Protection of Human Subjects, San Diego State University. Informed consent was obtained from all participants.

Reprint requests to Chris Peter, PhD, San Diego County Public Health Laboratory, P.O. Box 85222, San Diego, CA 92186-5222. E-mail: cpeterhe@co.san-diego.ca.us.

ABBREVIATIONS USED IN TEXT

BC = Baja California
MTB = *Mycobacterium tuberculosis* complex
SDC = San Diego County
TB = tuberculosis
ETH = ethambutol hydrochloride
INH = isoniazid
PZA = pyrazinamide
RIF = rifampin
STR = streptomycin sulfate

Baja California Patients (Descriptive Study)

During the period between February 1995 and May 1996, physicians based in public health TB clinics, community health centers, and hospitals as well as outreach workers in community settings recruited a convenience sample of patients for participation. Most of these patients (83%) were recruited through Servicios Coordinados de Salud Pública de B.C. and Instituto Mexicano Seguro Social which together serve 87% of the Baja California population.[3] Inclusion criteria consisted of

- Having a TB compatible X-ray film with at least one of the following symptoms: cough, sputum production, hemoptysis, fever of at least two weeks, or weight loss;
- Having a positive acid-fast smear;
- Being a symptomatic household contact of a diagnosed TB case;
- Having at least two of the following symptoms: cough, sputum production, hemoptysis, night sweats, and weight loss.

Patients under treatment for TB also were recruited, if they had received anti-TB medication ≤2 weeks or if they continued to have positive acid-fast smears four or more weeks after initiation of treatment with anti-TB medication. A total of 3,027 patients were recruited: 1,002 from Ensenada, 965 from Mexicali, and 1,060 from Tijuana. A single sputum specimen was obtained from each patient.

San Diego County Patients (Population-Based, Prospective Study)

All 331 TB patients with positive sputum cultures for MTB who were reported to the San Diego County Department of Health Services during the time period from February 1, 1995, to May 31, 1996, were studied.

Questionnaires and Patient Data

Survey data was collected from questionnaires used in interviewing patients and from public health case records. Data collected included treatment history, birth date, country and state of birth, place of residence five years ago, number in household, household income, and frequency of transborder travel and contact with residents from the opposite side of the border within the past 30 days. Subjects interviewed included each of the BC patients and 280 (85%) of the 331 reported SDC pulmonary TB patients. San Diego County patients previously diagnosed with TB were classified as previously treated.

Laboratory Testing

Sputum specimens from BC and most SDC patients were processed using the NaOH-NALC method, examined for acid-fast bacilli using the fluorochrome stain, and cultured on Lowenstein-Jensen slants, Middlebrook 7H10 agar plates, and Bactec 12B media using standard methods[4,5] at San Diego County and Imperial County Public Health Laboratories. Some specimens from SDC patients were cultured in clinical laboratories. Isolates of mycobacteria were identified using a combination of DNA probes (Gen-Probe, San Diego, CA), biochemical tests,[4] and in some cases, high performance liquid chromatography.[6]

MTB isolates were tested for susceptibility to 2.5 µg/mL ethambutol (ETH), 0.1 µg/mL isoniazid (INH), 100 µg/mL pyrazinamide (PZA); 2.0 mg/mL RIF, and 2.0 µg/mL streptomycin (STR) using the Bactec system.[5] Some drug susceptibility tests on isolates from SDC patients were performed in other laboratories using the proportional method[7] and comparable concentrations of drugs.

Statistical Analyses

Analyses were conducted using SPSS 7.0 software. The Pearson's Chi-square and the Fisher exact tests were used to identify various independent variables from the questionnaire responses that were significantly associated with drug resistance to individual or multiple drugs (dependent variables). Two tests were used to eliminate independent variables strongly associated with each other: tolerance of independent variables, and multicollinearity via a correlation matrix. The backward stepwise logistic regression model was used; that is, all independent variables were included initially, then variables not significantly related to the outcome were removed one at a time. The Hosmer and Lemeshow goodness-of-fit test was used to determine the reliability of odds ratios.

Results

MTB was isolated from a total of 427 BC patients. Of the 427 isolates from these patients, 419 were identified as *M. tuberculosis* and the remaining 8 as probable *M. bovis*. Drug susceptibility testing was completed on all 427 isolates. The 331 isolates from SDC patients were identified as follows: 205 *M. tuberculosis*, 4 *M. bovis*, and 122 MTB. Isolates from the group of 122 MTB isolates could not be further identified as *M. tuberculosis* or *M. bovis* because equivocal results were obtained with biochemical tests, the cultures became non-viable during storage, or the clinical laboratories that performed the cultures had discarded the isolates. There was no significant difference in drug resistance of isolates from SDC patients interviewed and drug resistance of isolates from patients unavailable for interviews (data not shown). Data on drug susceptibility of isolates to ETH, INH, and RIF were available for all SDC patients. Susceptibility results for PZA and STR were available on 89% of SDC isolates.

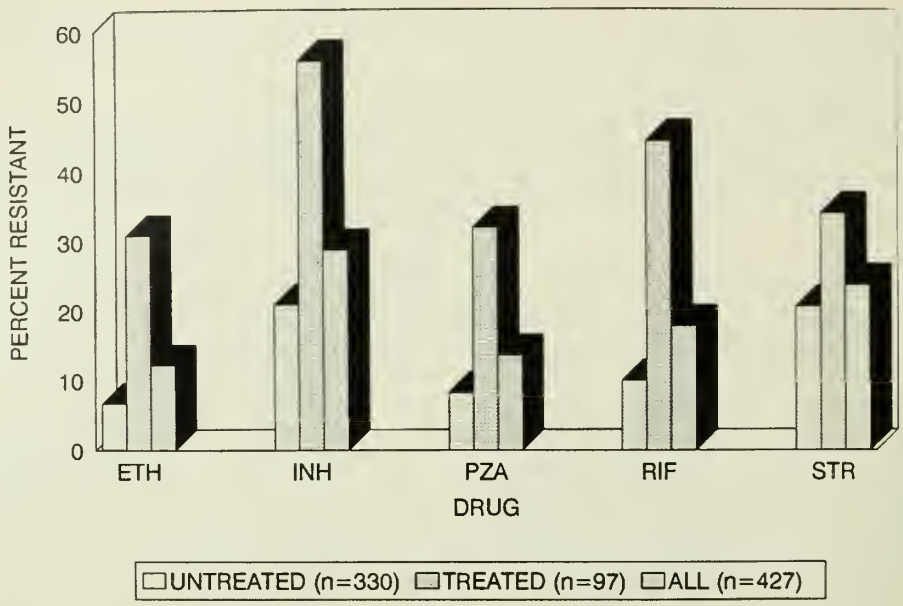


Figure 1.—Percentage of resistance among the individual *M. tuberculosis* complex isolates from 427 Baja California patients to each of the individual drugs is shown by patient treatment history. ETH = ethambutol hydrochloride, INH = isoniazid, PZA = pyrazinamide, RIF = rifampin, STR = streptomycin sulfate

Drug Resistance

Resistance of isolates from BC patients to the individual drugs by treatment history is shown in Figure 1. Overall resistance varied from 12.2% (52 of 427) to ETH to 28.8% (123 of 427) to INH. The percentages of patients with strains showing drug resistance to the individual drugs ETH, INH, PZA, and RIF were more than twice as high among patients with a history of previous treatment than those from patients with no prior treatment.

Overall resistance of isolates from the SDC patients varied from 1.5% (5 of 331) for ETH and RIF to 12.7% (42 of 331) for INH. As shown in figure 2, the proportion of isolates resistant to INH was 4-fold higher among

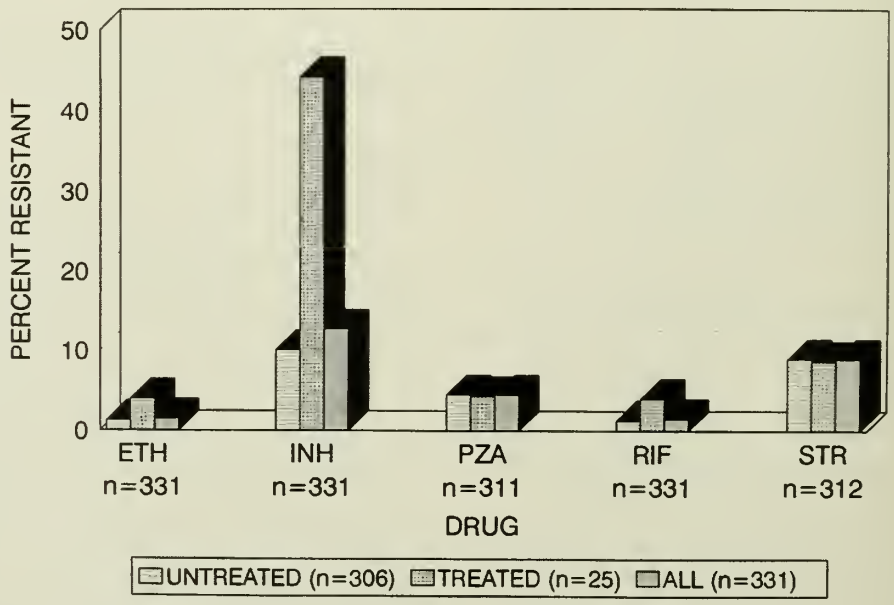


Figure 2.—Percentage of resistance among the *M. tuberculosis* complex isolates from San Diego County patients to each of the individual drugs is shown by patient treatment history. ETH = ethambutol hydrochloride, INH = isoniazid, PZA = pyrazinamide, RIF = rifampin, STR = streptomycin sulfate

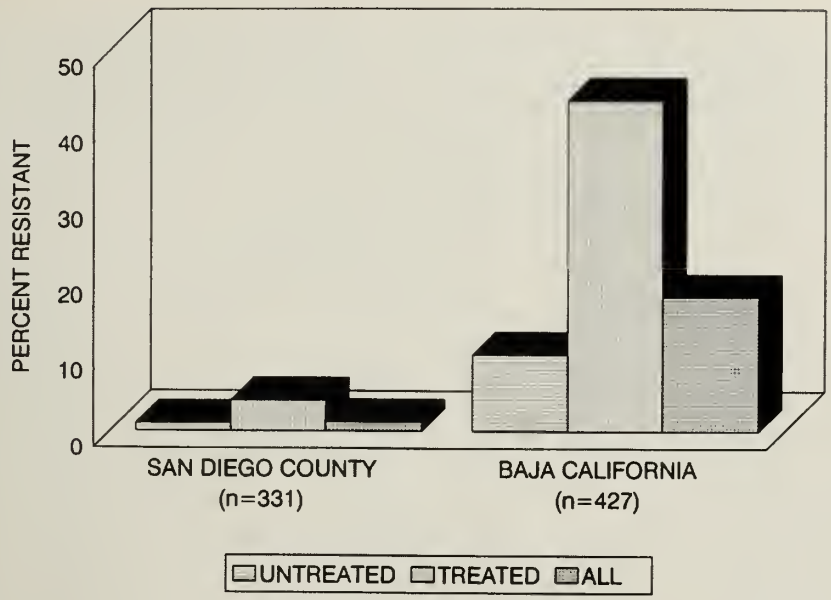


Figure 3.—Percentage of combined resistance to both isoniazid (INH) and rifampin (RIF) among the *M. tuberculosis* complex (MTB) isolates from Baja California and San Diego County patients are shown by patient treatment history.

those from patients with a history of previous treatment as compared to those from untreated patients.

Figure 3 shows frequency of drug resistance to both INH and RIF. Overall frequency of resistance to both drugs among SDC patients was 1.2%. However for the isolates from BC patients, resistance varied from 10% (33 of 330) of those without previous treatment to 43.3% (42 of 97) of those with a history of previous treatment.

Frequency of resistance to one or more drugs is shown in Table 1. Isolates from 59% of the BC patients and 80% of the SDC patients were susceptible to all primary drugs.

Transborder Contacts

As shown in Table 2, 42.2% (68 of 161) of culture proven TB patients from Tijuana reported having ≥4 hours of contact with one or more residents from the U.S. within the past 30 days. Of these 68 patients, 78% had positive acid-fast smears. Most of the contact occurred with U.S. residents who traveled to Tijuana. Less than 19% (47 of 257) of the patients surveyed from Ensenada and Mexicali reported contact with U.S. residents. Among SDC TB patients, 16% reported having contact with residents from Mexico. Eighteen of 57 (31.6%) SDC patients born in Mexico indicated that they had visited Mexico within the past 30 days.

Risk Factors for Drug-Resistant Tuberculosis Among TB Patients

Independent variables directly or indirectly associated with drug resistance and showing a good fit with the models are shown in Table 3. History of previous treatment was the only variable associated with increased odds of drug-resistant TB among residents on both sides of the border.

Discussion:

The data reveals substantially higher frequencies of drug-resistant pulmonary TB in BC than in SDC. The data on

TABLE 1.—*Multiple Drug Resistance*

Resistant to	*Patients from* Bajo California (n = 427)	Son Diego County (n = 293)
0 Drugs	59.4%	79.6%
1 Drug	17.1%	15.0%
2 Drugs	7.5%	3.4%
3 Drugs	4.9%	1.0%
4 Drugs	5.9%	0.3%
5 Drugs	5.2%	0.7%

TABLE 2.—*Reported Patient Contact Lasting ≥4 Hours with Residents from the Opposite Side of the Border within the Past 30 Days*

Patients from	*Any Transborder Contact*	*On the Same Side of the Border*	*On the Opposite Side of the Border*
Ensenada, Baja California (n = 81)	16.0%	14.8%	2.3%
Mexicali, Baja California (n = 176)	19.3%	14.2%	6.8%
Tijuana, Baja California (n = 160)	42.2%	39.1%	16.1%
San Diego County (n = 234)	15.8%	12.0%	10.3%

TABLE 3.—*Variables Associated with Increased or Reduced Odds of Drug Resistance*

Isolates of Patients from	*Resistance to*	*Variable*	*Odds Ratio*	*95% Confidence Interval*
Baja, California	INH	Previous treatment	3.30	2.01 - 5.44
	INH	Age	1.19	1.03 - 1.38
	INH	Recent contact ≥4 hrs. in BC with a California resident	0.47	0.26 - 0.86
	ETH	Previous treatment	2.99	1.59 - 5.64
	ETH	Recent contact ≥4 hrs. in BC with a California resident	0.49	0.21 - 1.16
	RIF	Previous treatment	4.58	2.60 - 8.04
	RIF	Age	1.19	1.00 - 1.41
	RIF	Recent contact ≥4 hrs. in BC with a California resident	0.40	0.19 - 0.86
	INH and RIF	Previous treatment	4.72	2.68 - 8.32
	INH and RIF	Age	1.19	1.00 - 1.41
	INH and RIF	Recent contact ≥4 hrs. In BC with a California resident	0.41	0.19 - 0.88
	> 1 Drug	Previous treatment	2.25	1.42 - 3.57
	> 1 Drug	Age	1.13	1.00 - 1.29
San Diego County	INH	Previous treatment	5.95	1.87 - 18.92
	INH	Age	0.83	0.68 - 1.02
	PZA	Hispanic ethnicity	4.86	1.45 - 16.24
	STR	Age	0.80	0.63 - 1.02
	> 1 Drug	Previous treatment	3.21	1.06 - 9.73
	> 1 Drug	Age	0.80	0.67 - 0.94

BC = Baja California; ETH = ethambutol hydrochloride; INH = isoniazid; PZA = pyrazinamide; RIF = rifampin; STR = streptomycin sulfate

frequency of drug resistance among the two populations, however, cannot be directly compared because the study of the BC patients was not a population-based study. Nevertheless, the magnitude of INH and RIF multidrug resistant TB (75 of 427) cases appears substantial compared to the few (4 of 331) cases in SDC. Data from the Pan American Health Organization collected in 1994 also has indicated substantially higher drug resistance rates among TB patients residing in Mexican border communities than in their nearby U.S. sister cities.[2] The Pan American Health Association statistics recorded 29% of TB cases as drug resistant in San Luis Rio Colorado, Sonora, compared to 4% in nearby Yuma, Arizona; 30% in Tijuana, BC, but 20% in San Diego, California; and 56% in Nuevo Laredo, Tamaulipas, with 16% in Webb County, Texas. While these data were not determined using population-based studies, they do suggest that a relatively high proportion of TB patients residing in BC Mexican border communities are infected with drug resistant MTB.

A study by Sifuentes-Osornio and co-workers[8] of MTB isolates from 84 patients, mostly from the Mexico City region, reported a similar proportion of isolates resistant to individual primary drugs as we found among BC patients: ETH, 10%; INH, 24%; RIF, 19%; STR, 12%; and combined resistance to INH and RIF, 20%. They found that 70% of isolates, a higher proportion than our figure of 59%, were susceptible to all drugs evaluated. However, they did not test for PZA susceptibility. Another notably higher proportion of drug-resistant isolates, 70%, was reported by Alvarez-Gordillo et al. among 18 patients in the Mexican state of Chiapas.[9] Possible reasons for differing proportions of patients with drug resistant TB among different regions of Mexico are non-random sampling of patients and varying resources for detection of cases and ensuring completion of treatment. A population-based study being conducted by the U.S. Centers for Disease Control and Prevention and the Instituto Nacional de Diagnóstico y Referencia Epidemiológicos of Mexico in several Mexican states may provide a more comprehensive picture of the prevalence of drug resistant TB in Mexico (R. Granich, MD, U.S. Centers for Disease Control and Prevention, personal communication, December 1997).

Within the U.S. there is also variation in the percentage of drug resistant TB cases reported by individual states, although the variation is not as pronounced as reported within Mexico. The percentage of SDC pulmonary TB patients infected with INH resistant strains, 12.7%, is higher than the 1996 figures for all reported TB patients in California (9.8%), Arizona (5.9%), Texas (5.4%), and nationally (8.0%).[10]

Our data, demonstrating that 32% of Mexican born SDC TB patients surveyed had visited Mexico within the past 30 days, is consistent with a previous study conducted by the U.S. Centers for Disease Control and Prevention. They demonstrated that 35% of foreign-born Hispanic TB patients residing in U.S. border communities visit their country of origin, primarily Mexico, at least monthly.[11] Our report is the first that documents transborder contact between Mexican residents with TB and persons residing in the U.S. The reported contact of 68 smear-positive Tijuana patients with residents from the U.S. indicates a potential for international transmission. The notable finding that 15.8% (37 of 234) SDC TB patients reported contact with BC residents estab-

lishes that TB transmission across the border is likely to be bidirectional, south to north as well as north to south. However, the extent of such transmission is difficult to demonstrate without availability of longitudinal DNA fingerprinting data and epidemiological investigation of isolates with matching fingerprints.

The relationship between previous treatment and both drug resistant and multiple drug resistant TB has been well documented by others.[12-14] The tendency for BC patients to have an increased risk of TB resistant to >1 drug with increasing age could be related to an increased chance of exposure to someone with drug-resistant TB over time. In addition, some patients may have undertaken unreported, self prescribed, ineffective TB treatment. Arevalo et al. noted that patients over age 45 in Spain had an increased risk of drug-resistant TB.[14] The higher risk of younger SDC patients for TB resistant to ≥1 drug may reflect more recent infection during a time when drug resistant TB is more prevalent worldwide. The connection of Hispanic ethnicity to PZA resistance among SDC patients may stem from the fact that *M. bovis*, which is inherently resistant to this drug, is most commonly associated with the Hispanic population in SDC.[15]

Others have linked drug-resistant TB with additional risk factors, including cavitary lung disease,[17,18] HIV infection,[16,19] hepatic cirrhosis,[14] and homelessness.[19] However, our study did not attempt to evaluate these factors because of difficulty in obtaining the information. Although foreign-born individuals have been reported to have increased rates of drug-resistant TB,[16,18] foreign birth was not implicated as an independent risk factor in the SDC patient population, possibly because of sample size, the large proportion (78%) of the SDC patients who were foreign born, or the commonness of other risk factors among foreign-born patients.

Although this study was not designed to document transborder transmission of TB, 42% of Tijuana patients and 16% of SDC patients had recent contact lasting ≥4 hours with residents from the opposite side of the border. Further studies are needed to determine the amount of transmission caused by this type of contact, but our findings suggest that coordinated binational efforts may be important for TB control in this border region.

Acknowledgments

The following individuals contributed to this report: Nancy Cohee; Elba Cornejo, MD; Concepcion Corona Rubio, MD; Roberto Escalante, MD; Juan Frias, MD; Louise Gresham, PhD; Elizabeth Haas, MPH; Dawn Kiefler; Jose Lepe, MD; David Ontiveros, MD; Pablo Lopez Romero, MD; Azi Maroufi, MPH; Fernando Marin Padilla, QFB; Blanca Ramirez, RN; Lori Senini, RN; Jesus Tiznado Farrell, MD; Dolores Torres Uribe, MD; and Graciela Zuniga-Groot.

REFERENCES

1. Cox M. Regents of the University of California and Colegio de la Frontera Norte (data disk). San Diego/Tijuana Economic Review 1996;

2. Escobedo ME, de Cosio FG. Tuberculosis and the U.S.-Mexico border. J Border Health 1997; 2:40-47

3. Sistema Nacional de Salud, Mexico. Boletin de Información Estadística. 1994; 14:11

4. Kent PT, Kubica GP. Public health mycobacteriology: A guide for the level III laboratory. Centers for Disease Control 1985

5. Siddiqi SH. Bactec 460TB System product and procedure manual. Becton Dickinson and Company 1995

6. HPLC Users Group. Standardized method for HPLC identification of mycobacteria. Centers for Disease Control and Prevention 1996

7. Kubica GP, Dye WE. Laboratory methods for clinical and public health mycobacteriology. U.S. Government Printing Office, Washington D.C. 1967

8. Sifuentes-Osornio J, Ponce-de-Leon, LA, Camacho-Mezquita FE, Bobadilla-del-Valle JM, Infante-Suarez ML, Ramirez-Fernandez N, et al. Resistance of *Mycobacterium tuberculosis* in Mexican patients. I. Clinical features and risk factors. Rev Invest Clin 1995; 47(4):273-281

9. Alvarez-Gordillo GC, Halperin-Frisch D, Blancarte-Melendres L, Vazquez-Castellanos JL. Risk factors for antitubercular drug resistance in Chiapas, Mexico. Salud Publica Mex 1995; 37(5):408-416

10. Centers for Disease Control and Prevention: Reported tuberculosis in the United States, 1996. 1997; 26.

11. Centers for Disease Control and Prevention: Characteristics of foreign-born hispanic patients with tuberculosis — Eight U.S. counties bordering Mexico, 1995. MMWR 1996; 45:1032-1036

12. Grandes G, Lopez de Munain J, Diaz T, Rullan JV. Drug-resistant tuberculosis in Puerto Rico, 1987-1990. Am Rev Resp Dis 1993; 148(1):6-9

13. Mendoza MT, Gonzaga AJ, Roa C, Velmonte MA, Jorge M, Montoya JC, et al. Nature of Drug resistance and predictors of multidrug-resistant tuberculosis among patients seen at the Philippine general hospital, Manila, Philippines. Int J Tuberc Lung Dis 1997; 1(1):59-63

14. Arevalo M, Solera J, Cebrian D, Bartolome J, Robles P. Risk factors associated with drug-resistant Mycobacterium tuberculosis in Castilla-la-Mancha. Eur Respir J 1996; 9(2):274-278

15. Dankner WM, Waecker NJ, Essey MA, Moser K, Thompson M, Davis CE. *Mycobacterium ovis* infections in San Diego: a clinicoepidemiologic study of 73 patients and a historical review of a forgotten pathogen. Medicine 1993; 72(1):11-37

16. Moore M, Onorato IM, McCray E, Castro KG. Trends in drug-resistant tuberculosis in the U.S., 1993-1996. JAMA 1997; 278(10):833-837

17. Saloman N, Perlman DC, DePalo VA, Kolokathis A, Wilets I. Drug-resistant tuberculosis: factors associated with rise in resistance in an HIV-infected urban population. Mt Sinai J Med 1994; 61(4):341-348

18. Riley LW, Arathoon E, Loverde VD. The epidemiologic patterns of drug-resistant Mycobacterium tuberculosis infections: a community-based study. Am Rev Respir Dis 1989; 139(5):1282-1285

19. Kent JH. The epidemiology of multidrug-resistant tuberculosis in the U.S. Med Clin North Am 1993; 77(6):1391-1409

Conferences and Reviews

Health and Safety Risks in Production Agriculture

SUSANNA G. VON ESSEN, MD, *Omaha, Nebraska, and* STEPHEN A. McCURDY, MD, *Davis, California*

Production agriculture is associated with a variety of occupational illnesses and injuries. Agricultural workers are at higher risk of death or disabling injury than most other workers. Traumatic injury commonly occurs from working with machinery or animals. Respiratory illness and health problems from exposures to farm chemicals are major concerns, and dermatoses, hearing loss, certain cancers, and zoonotic infections are important problems. Innovative means of encouraging safe work practices are being developed. Efforts are being made to reach all groups of farmworkers, including migrant and seasonal workers, farm youth, and older farmers.

(Von Essen SG, McCurdy SA. Health and safety risks in production agriculture. West J Med 1998; 169:214–220)

Agriculture is a major industry in the United States. About 10 million people work in production agriculture. These include owner-operators and their families, full-time employees, migrant and seasonal workers, and persons who regularly work on farms, such as veterinarians and crop consultants.

As consumers, we know of the variety of agricultural products. Many people, however, including some health care professionals, do not realize that production agriculture is associated with a risk of injury and illness greater than that of most other industries. Agriculture is unique because these risks affect many children and elderly persons as well as workers between the ages of 18 and 65 years.[1–4]

Farmers and farmworkers are at greater risk of traumatic death and disabling injury than workers in all industries except mining.[5] According to the National Safety Council, the number of fatalities has greatly decreased in recent years in mining and construction but has fallen only slightly in agriculture.[6] Risks of acute pesticide poisoning and long-term effects of pesticide exposure such as lymphoid malignant neoplasms are present in a variety of settings where crops are grown. Respiratory disorders develop from the inhalation of grain dust, other types of organic dusts, and work in animal confinement facilities. Hearing loss is an important problem in settings where machinery is in use. Skin cancers caused by sun exposure are a serious problem. Irritant and allergic dermatoses occur from exposures to plants and farm chemicals. Zoonotic infections can cause life-threatening illness. Heat and cold stress occur from exposure to the elements.

In recent years, efforts have increased to characterize and reduce these hazards. Interventions have included engineering innovations, legislation, education programs, and improved occupational medicine services for farmers.[7,8] Programs are being developed to provide insurance incentives for farming more safely.[9,10] The increasing number of corporate farms, which do not employ children and which often have safety programs, may reduce the risk for farm workers. A great need still exists for changes that will further reduce the number of occupational injuries and illnesses related to production agriculture.[11] In this article, we review the major health and safety risks in production agriculture.

Agricultural Workers

There are few data describing the size and characteristics of agricultural populations, and great disparities exist in figures given by different sources, especially for hired laborers. The 1992 Census of Agriculture reports 3,801,878 directly hired farm laborers on the nation's 1,925,300 farms.[12] Martin and others have estimated there are about 2.5 million hired farmworkers in the United States, of whom about 2.0 million are involved in crop production.[13,14] About 900,000 of these are migrant and seasonal workers, two thirds of whom shuttle from a fixed location outside the United States and stay for the season ("shuttle migrants"); about a third travel to follow crop employment.[14]

Hired farm laborers are especially difficult to count because of the social, economic, and linguistic margin-

From the Department of Internal Medicine, Pulmonary and Critical Care Section, University of Nebraska Medical Center, Omaha (Dr Von Essen); and the Department of Epidemiology and Preventive Medicine, University of California–Davis (Dr McCurdy).

Reprint requests to Susanna G. Von Essen, MD, Department of Internal Medicine, Pulmonary and Critical Care Section, University of Nebraska Medical Center, Box 985300, Omaha, NE 68198-5300 (e-mail: svonesse@unmc.edu).

alization characteristic of this population.[15] The Bureau of Labor Statistics reports an average annual employment in 1996 of 752,200 persons in production agriculture.[16] The 1990 Census indicates 182,235 migrant and seasonal farm workers in California, yet figures based on employment, average crop-specific labor demand, and crop volume statistics suggest a population size between 563,000 and 720,000—an undercount by the census of about 60% to 70%.[13]

Migrant farmworkers tend to follow three main migration streams: the eastern stream comprising the Atlantic seaboard, the midwestern stream comprising Texas through the midwestern states, and the western stream based in California and Arizona and ranging up to Oregon and Washington.[17] The eastern stream is the most ethnically diverse and includes African Americans, Caribbean peoples, and Hispanics. About 90% of the workers in the midwestern and western streams are Hispanic.[17]

The National Agricultural Workers Survey provides useful demographic information on the farmworker population.[18] The population is predominantly young men and overwhelmingly Hispanic, Spanish speaking, and foreign born. Mexico is the most common place of birth. Farmworkers typically have a seventh-grade education and have spent 10 to 12 years in agriculture. California farmworkers work an average of 35 weeks per year in agriculture and two additional weeks per year in nonagricultural jobs. The median family income is between $10,000 and $12,499. Individual incomes are about half this figure and lowest among unauthorized workers. Nearly half of farmworkers live in poverty. Despite these extreme circumstances, farmworkers infrequently use social support programs. About 13% of California seasonal agricultural workers reported using social support programs, primarily food stamps.[19] In the 1990-1991 California survey, about 9% were unauthorized to work in the United States. More recent data from the workers survey show that about 37% of agricultural workers were unauthorized.[18] The most likely reason for this pronounced increase in unauthorized workers is that the Immigration Reform and Control Act of 1986 conferred citizenship on noncitizens with work authorization, who then left agricultural employment. This created a demand for workers and drew illegal immigrants, primarily from Mexico. Economic instability in Mexico has also contributed to such immigration.

Traumatic Injury

Work injury data are not as readily available for agriculture as for other industries. The reasons for this are varied, including that most American farms do not fall under the reporting requirements of the Occupational Safety and Health Administration because they do not have 11 or more employees. Also, many persons who work on farms are not covered by workers' compensation insurance systems.[1,20,21] Death certificates have been widely used to identify fatal injuries on farms. This practice has been found to lead to an underestimation of the number of such deaths.[22]

A number of well-designed studies conducted recently have documented a high rate of traumatic injury in farmworkers. Injury rates reported range from 9.6% to 16.6% per year.[23–28] The greatest number of injuries occurred in the seasons during which crops are grown and harvested. The use of machinery and animal handling were important causes of traumatic injury, as were falls. Dairy farming, a type of agriculture that involves extensive animal handling, is associated with a high risk for injury. Machinery injuries most often include trauma to the hand and eye.[29] The power takeoff, a device used to transfer energy from a tractor to farm equipment, is a common source of serious injury if it is not fitted with a safety shield. Machinery trauma includes high-pressure–injection injuries from devices, such as grease guns, and these require emergent surgical decompression.[30] Farm chemical exposures to anhydrous ammonia and other caustic substances are another cause of severe eye injuries.[31] Death from electrocution is fairly common.

Fatalities associated with farm tractors are the most common cause of work-related death in the US agricultural industry.[32] Most fatalities occurred from tractor rollovers or run overs. Fatal injuries from tractor rollovers are much more likely to occur if the tractor does not have a rollover protection structure. A great deal of effort is being made to provide incentives and means for farmers to retrofit older tractors with rollover protective structures. Legislation requiring rollover protective structures on tractors has been successful in nearly eliminating tractor rollover deaths in Sweden.[33] Despite this, less than half of US tractors are equipped with rollover protection structures.[34]

Respiratory Illness

Various respiratory disorders occur in agricultural workers.[35] The disorders are a common problem in this group of workers and are a cause of substantial morbidity. These disorders overlap considerably. For example, in a worker who has had farmer's lung, chronic bronchitis may develop as a complication.

Exposures that play an important role in causing respiratory disorders include grain dust, dust and gases in animal confinement units, mold and thermophilic bacteria in hay and grain, and silo gas. Many of the bioaerosols inhaled by agricultural workers are rich in endotoxin, which has been associated with both acute and chronic illness. Evidence exists that other substances in the organic dust, including mycotoxins and silica, play an important role as well.[36,37]

Acute respiratory illnesses include organic dust toxic syndrome, a febrile, influenza-like illness that occurs 4 to 12 hours after exposure and is self-limiting.[38] This problem develops in about a third of grain and livestock farmers at some time. The syndrome is associated with heavy organic dust exposure, usually to grain dust or a swine confinement building.[35,36] Its symptoms resemble those of a far less common problem, farmer's lung. The symptoms also resemble those of metal fume fever, a

disorder seen in welders working with galvanized metal in the agriculture setting and elsewhere.

Farmer's lung is one of many forms of hypersensitivity pneumonitis.[39] This problem is becoming rare, which is likely due to the reduction of exposure to organic dust from the increasing mechanization of agriculture and the effect of farm health and safety programs. Acute farmer's lung is characterized by dry cough, fever, and malaise four to eight hours after exposure to a substance to which the worker has been sensitized. The onset of the subacute form may be less clearly linked to a specific exposure. Biopsy of lung specimens taken in the acute and subacute phase are notable for the presence of noncaseating granulomas and a mixed population of inflammatory cells. These forms of farmer's lung respond to treatment with oral corticosteroids.[40] A chronic form of farmer's lung also exists that is characterized by the presence of pulmonary fibrosis that cannot be distinguished from fibrosis with other causes. The pulmonary fibrosis associated with farmer's lung may lead to respiratory failure and death.[41]

Chronic bronchitis is more common in agricultural workers than in the general population.[42–45] The prevalence of this disorder ranges from 3% to 30% of nonsmoking farmers in the populations studied. Causes for this problem include exposure to grain dust and the animal confinement unit environment. The findings of spirometry may be signs of airways obstruction in these workers, or they may be unremarkable. Inflammation and respiratory tract symptoms can also be seen after acute, heavy exposures of this type.[46,47] These forms of bronchitis infrequently cause severe respiratory impairment unless an agricultural worker also smokes cigarettes; the adverse effects of the farm environment and cigarette smoking on lung function are additive.

Animal confinement workers are at risk for an asthmalike syndrome characterized by chest tightness, cough, and dyspnea with exertion. Various studies have shown that 2% to 40% of workers have symptoms of the asthmalike syndrome on a daily basis. The asthmalike syndrome is not related to atopy. Risk factors include increasing age; working in swine confinement units for at least six years; and exposure to high levels of ammonia, endotoxin, total dust, and respirable dust in the barns.[48] The results of spirometry are usually normal in these workers, but they commonly have a cross-shift decrease in the forced expiratory volume in one second. These workers also commonly have an irritant rhinitis.

According to most studies, the prevalence of asthma in agricultural workers is similar to that in other populations.[49,50] Even though many farmworkers are sensitized to substances in their work environment, no clear evidence exists that exposure to those substances in the work setting causes asthma. Farmworkers who have asthma are at increased risk of suffering exacerbation of their asthma after exposure to dusts and fumes.

Toxic gas exposures, which can be fatal, are another important respiratory problem in production agriculture. Silage stored in concrete silos may release nitrogen dioxide for several weeks after the silo is filled.[51] Nitrogen dioxide may cause death in a matter of minutes with heavy exposure. Exposure at lower levels may cause acute respiratory tract symptoms, and bronchiolitis obliterans may develop weeks later. The bronchiolitis obliterans responds to treatment with corticosteroids. Some silos are oxygen-limiting, and entering these structures can result in asphyxiation.

Animal wastes are frequently stored underground and are a source of toxic gases. Entering confined spaces used for manure storage can lead to fatalities, which are often caused by hydrogen sulfide exposures.[52]

Entrapment and suffocation in stored grain is an important problem in production agriculture. Measures such as wearing a safety harness and not working alone help reduce the risk of death when handling stored grain.[53]

Environmental controls are important for preventing respiratory illness in agricultural workers. These include measures to reduce dust, such as increased ventilation and the use of canola oil sprinkled to reduce dust in the air in swine confinement buildings.[54] Workers should also use respirators to reduce dust exposure. Evidence exists that the risk of episodes of farmer's lung is substantially reduced by wearing a respirator.[55] Mechanical filter respirators may be disposable paper masks or may consist of a rubber or plastic face piece and replaceable filter elements. These respirators should not be confused with the nuisance dust masks commonly available in hardware stores. Disposable respirators used in agricultural settings should have two straps for optimal fit and should be certified by the National Institute for Occupational Safety and Health as being suitable for use against dust and mists. Powered air-purifying respirators offer more protection than the other types of respirators and reduce the physical stress of wearing these devices.[56] Entering confined spaces with possibly toxic gas levels should be avoided if possible. The use of proper equipment with an air supply is essential for entering spaces known or suspected of containing dangerous levels of hydrogen sulfide, nitrogen dioxide, or other toxic gases.

Hearing Loss

Farmers are regularly subjected to loud noises when working with machinery such as tractors, feed grinders, and chain saws.[57,58] Noise made by large animals such as pigs can be loud enough to damage hearing.[59] Hearing loss has been documented as early as the teenaged years in farm youth.[60] As with other industries where high levels of noise are a problem, the noise-induced hearing loss initially occurs in the region of the cochlea responsible for higher frequencies. If noise exposure continues, the hearing loss extends to lower and higher frequencies, making normal human speech difficult to understand. In a recent study, 65% of dairy farmers had hearing loss. Screening audiograms to identify affected persons, engineering controls to reduce noise exposure, education programs, and the use of hearing protection are an important part of occupational health services for farmworkers.

Cancer

The overall cancer risk for farmers is lower than for the general population. The risk for common cancers such as those of the lung and colon is lower in farmers.[61,62] That for several types of cancer, however, is increased in farmers, including leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, and cancers of the lip, stomach, skin, prostate, brain, and connective tissue. With the exception of cancer of the lip, the relative risk for these cancers is fairly low but has been identified in most studies of cancer in agricultural workers. Evidence exists that ongoing exposure to pesticides, insecticides, herbicides, and fungicides may be linked to an elevated relative risk for some cancers,[63] but not all studies find a relationship between exposure to farm chemicals and cancer.

Farm Chemical Poisoning

Pesticide exposure can cause serious illness and death. Illness from pesticide exposure is likely frequently not recognized or reported as being linked to this exposure. Various pesticides can cause acute illness.[64] Organophosphates irreversibly block the enzyme acetylcholinesterase, causing acetylcholine to accumulate at nerve synapses and the neuromuscular junction and leading to excess parasympathetic stimulation. Signs and symptoms of organophosphate poisoning include bradycardia, hypotension, salivation, lacrimation, urinary incontinence, diarrhea, vomiting, abdominal cramping, bronchospasm and bronchorrhea, muscle fasciculations and weakness (which can cause respiratory failure), confusion, hallucinations, seizures, and coma. Treatment of this problem includes the anticholinergic agent atropine sulfate and oximes such as pralidoxime chloride, which are used to displace the organophosphate from cholinesterase.

Long-term exposure to organophosphates is seen in farmworkers such as orchard sprayers and in other groups. Symptoms include headache, nausea, weakness, fatigue, and chest tightness. Evidence is increasing that long-term organophosphate exposure can cause permanent neurologic deficits,[65] including peripheral neuropathy and deficits in memory, attention, and motor skills.

Biomarkers of exposure to organophosphates include cholinesterase levels in plasma and erythrocytes. Levels should be determined at baseline and at the time of suspected poisoning. Moderate symptoms may be expected with a 60% to 90% reduction in levels from baseline.

Carbamate insecticides cause a reversible inhibition of cholinesterases with symptoms similar to those of organophosphate poisoning. Treatment consists of the administration of atropine.

Pyrethrin and pyrethroid insecticides are substances that have a better safety profile than do organophosphates and carbamates, but they can also cause severe symptoms and death.

A variety of herbicides and fungicides in common use can cause serious systemic symptoms. These include 2,4-dichlorophenoxyacetic acid and paraquat. The ingestion of paraquat may result in fatal pulmonary fibrosis and renal failure.

The key to avoiding poisoning from farm chemicals is the safe storage of these substances and the use of proper personal protective equipment. Accurate records must be kept regarding farm chemical use. Also, pesticide-contaminated clothing must be laundered separately from other clothing.

Anhydrous ammonia is widely used as a fertilizer. Common injuries from anhydrous ammonia exposure include eye and skin burns and injury to the larynx.[67,68] Long-term impairment from lower respiratory tract injury can occur.

California is unique among the states in maintaining reporting systems for pesticide use and pesticide illnesses. In 1990, California instituted full-use reporting for pesticides, requiring monthly reporting to county agricultural agents.[69] Reports include the date and location (section, township, and range) where the application was made, the crop, and the kind and amount of pesticides used. The primary exceptions to the full-use reporting requirements are home and garden use and most industrial and institutional uses. In 1995, 211,798,752 lb (active ingredient) were used. Of this total, 192,471,136 lb (90.9%) were used in production agriculture.[69,70]

California has required the reporting of pesticide-related illnesses since 1971.[71] Reported cases are categorized with respect to pesticide causation as definite, probable, possible, unlikely, or indeterminate. In 1995, 1,593 illnesses occurred that had a possible or confirmed link to pesticide use. Of these, 656 (41.2%) cases occurred in agricultural settings. In 1995, the latest year for which published data are available, 1,117 definite or probable pesticide-related injuries or illnesses occurred in California. Unfortunately, published data do not separate the agricultural cases from this total. Exposure to pesticide aerosol from spraying ("drift") was the most commonly reported exposure circumstance and occurred in 277 (24.8%) cases. The use of applicator equipment was associated with 251 (22.5%) cases. Definite or probable cases included 12 persons admitted to a hospital (totaling 54 reported hospital days) and 212 persons suffering disability days (totaling 883 days). No agriculturally related pesticide fatalities occurred. Insecticide combinations were associated with 142 definite or probable cases, organophosphates were associated with 103 cases, and fumigants were associated with 92 definite or probable cases.

Risk factors for severe organophosphate-related illness (that is, associated with disability or hospital admission) include direct exposure to residue (odds ratio, 4.6), work as mixer-loader or applicator (odds ratio, 4.1), and Spanish surname (odds ratio, 1.6).[72] The use of diethyl organophosphates (versus dimethyl organophosphates) was also associated with increased severity.

Dermatoses

Occupational skin disorders are common in agricultural workers. The effects of sun exposure are an important cause of morbidity in this occupational group, particular-

TABLE 1.—*Zoonotic Diseases Of Occupational Significance In Agricultural Workers*

Disease	*Organism*	*Exposure*	*Management*
Anthrax	*Bacillus anthracis*	Cattle	Penicillin
Encephalitis	Arboviruses	Horses, mosquitos	Supportive care
Lyme disease	*Borrelia burgdorferi*	Tick *Ixodes ricinus*	Tetracyclines or penicillin
Brucellosis	*Brucella abortis*	Cattle	Tetracyclines and streptomycin or doxycycline and rifampin
Gastroenteritis	*Campyelobacter* species	Sheep, cattle	Erythromycin
Spontaneous abortion	*Chlamydia trachomatis* and *Chlamydia psittaci*	Lambing sheep	Avoidance
Pneumonia	*C psittaci*	Turkeys, chickens	Tetracyclines
Q fever, endocarditis	*Coxiella burnetii*	Sheep, cattle	Tetracyclines
Tetanus	*Clostridium tetani*	Soil contaminated with animal feces	Supportive care
Diarrhea	*Cryptosporidium parvum*	Water contaminated by cattle feces; Cats, dogs	No effective therapy
Hydatid disease	*Echinococcus* species	Sheep, dogs	Resection
Tularemia	*Francisella tularensis*	Sheep	Streptomycin or gentamicin sulfate
Respiratory failure	Hantavirus	Rodents	Supportive care
Leptospirosis, spontaneous abortion	*Leptospira* species	Exposure to cattle, pigs, rodents	Penicillin, avoidance
Listeriosis, meningitis	*Listeria monocytogenes*	Cattle, sheep, goats, fowl	Penicillins
Cellulitis	*Pasteurella multocida*	Bites by cats,dogs	Penicillin
Rabies	Rabies virus	Infected mammals	Supportive care
Salmonellosis	*Salmonella typhimurium*	Sheep, cattle	Supportive care
Meningitis	*Streptococcus suis*	Pigs	Penicillin
Toxoplasmosis	*Toxoplasma gondii*	Cats, fur-bearing animals, raw pork and mutton	Pyrimethamine, sulfadiazine
Ringworm	*Trichophyton* species	Small mammals	Topical antifungals

ly in those with fair skin.[73] Persons who sunburn easily are at increased risk for skin cancers. The most common type of skin cancer in agricultural workers and in the general population is basal cell carcinoma. Lip cancer is also more common in agricultural workers, as is squamous cell carcinoma. The relative risk for the development of nonmelanoma skin cancers in farmers ranges from 0.8 to 1.8 and for lip cancer from 1.3 to 3.1.[61] The risk for melanoma apparently is also increased for this occupational group, with the relative risk in various studies ranging from 0.5 to 6.3. Preventive efforts have included encouraging the routine use of sunscreens and the wearing of broad-brimmed hats instead of baseball-style caps.

A variety of farm chemicals and materials used for veterinary care can cause allergic contact dermatitis. Important causes of this problem include many pesticides, fertilizers, topical antibiotics designed for veterinary use, and latex.

Zoonoses

A long list of pathogens can cause zoonotic disease in agricultural workers, including bacteria, viruses, rickettsiae, chlamydiae, parasites, and fungi.[74–79] The zoonotic disorders range in severity from fungal infections such as ringworm that are easily treated to life-threatening problems like rabies or anthrax (Table 1). Measures to prevent these infections include maintaining the health of farm animals, avoiding skin contact with animals known to be infected, and wearing respirators approved by the National Institute for Occupational Safety and Health when working in high-risk situations where diseases such as brucellosis and Q fever may be contracted by inhalation.

Heat and Cold Stress

Because farmworkers spend a great deal of time outdoors, they are at risk for physical stress from excessively cold and excessively hot environments.[80] The magnitude of heat and cold stress problems in agriculture is not well documented. Tolerance to such environments varies among individuals and may be difficult to predict.[81] Agricultural workers should be provided the means to compensate for extremes of temperature. For example, adequate water supplies while working outdoors in hot climates are essential.

Musculoskeletal Disorders

Agricultural production labor is often physically demanding and may involve repetitive motions, characteristics associated with an increased risk for acute and chronic musculoskeletal disorders. In California, workers' compensation data show that sprains and strains make up more than 40% cases of lost work.[82]

Few data are available that address chronic musculoskeletal condition among agricultural workers in specific commodities. In a recent study, 71% of swine producers reported chronic back problems.[83] Osteoarthritis of the hip and knee are common problems among New York dairy farmers.[84] An increased risk for shoulder pain has been demonstrated among greenhouse tomato workers[85] and orchard farmers harvesting pears and apples.[86] Overhead work requiring arm and head elevation was associated with an increased risk for shoulder-neck complaints.[86]

The prevention of musculoskeletal conditions requires eliminating or reducing exposure to highly demanding, repetitive tasks. New production methods to reduce exposures, however, may not be acceptable to employers or workers. Methods that reduce production or increase costs are unlikely to be accepted unless there is a clear and offsetting reduction in injury-related costs. Workers take pride in being among a select group able to perform difficult jobs; they may not accept innovations that open their employment to a wider field of potential competitors for their work.[87]

Green Tobacco Sickness

Workers harvesting tobacco by hand are known to suffer from an illness that consists of nausea, vomiting, weakness, diarrhea, headache, and dizziness.[88] This problem is caused by the dermal absorption of nicotine during the harvest process.

Conclusion

Work in production agriculture is associated with a wide variety of health hazards. The US farm-work–related death rate has fallen in the past 30 years, but there is still a great need for effective programs that will further reduce the risk of injury and illness on our nation's farms.

Acknowledgment

Dr. McCurdy is supported in part by the National Institute for Occupational Safety and Health (NIOSH #5 R01 OH03444-02) and the University of California Agricultural Safety and Health Center at Davis (NIOSH # 407/CC906162).

REFERENCES

1. Purschwitz MA, Field WE. Scope and magnitude of injuries in the agricultural workplace. Am J Ind Med 1990; 18:179–192

2. Cogbill TH, Steenlage ES, Landerscasper J, Strutt P. Death and disability from agricultural injuries in Wisconsin: a 12 year- experience with 739 patients. J Trauma 1991; 31:1632–1637

3. Schenker MB, Lopez D, Wintemute G. Farm-related fatalities among children in California, 1980–1989. Am J Public Health 1995; 85:89–92

4. Rivara FP. Fatal and non-fatal farm injuries to children and adolescents in the United States 1990–1993. Sponsored by Farm Safety 4 Just Kids. Seattle: University of Washington, Harborview Injury Prevention and Research Center and the Departments of Pediatrics and Epidemiology; 1997

5. Accident Facts. Itasca (Ill): National Safety Council; 1996

6. Report to the nation. Agricultural Occupational and Environmental Health: Policy Strategies for the Future. 3rd edition. National Coalition for Agricultural Safety and Health (Iowa City, Iowa); 1989

7. Aherin RA, Murphy DJ, Westaby JD. Reducing Farm Injuries: Issues and Methods. St Joseph (Mich): American Society of Agriculture and Engineering; 1992

8. Donham KJ, Thu KT. Agricultural medicine and environmental health: the missing components of the sustainable agriculture movement. In: McDuffie HH, Dosman JA, Semchuk KM, Olenchock SA, Senthilselvan A, eds. Agricultural Safety and Health. Boca Raton (Fla): CRC Press; 1995, pp 583–589

9. Shutske JM, Ohmans PJ. Shifting the paradigm: rethinking our approach to agricultural safety and health issues. J Agromed 1995; 2:39–44

10. Von Essen SG, Thu K, Donham KJ. Insurance incentives for safe farms. J Agromed; in press

11. Schenker MB. Preventive medicine and health promotion are overdue in the agricultural workplace. J Public Health Policy 1996; 17:275–305

12. US Dept of Commerce: 1992 Census of Agriculture. Vol 1, Geographic Area Series. Part 51: US Summary and State Data. Washington (DC): Economics and Statistics Administration, Bureau of the Census; 1994

13. Gabbard S, Kissam E, Martin PL. The Impact of Migrant Travel Patterns on the Undercount of Hispanic Farmworkers. Research Conference on Undercounted Populations. Washington (DC): Dept of the Census; 1993, pp 207–245

14. Martin PL, Martin DA: The Endless Quest: Helping America's Farm Workers. Boulder (Colo): Westview Press; 1994

15. McCurdy S. Occupational health status of migrant and seasonal farmworkers. In: McDuffie HH, Dosman JA, Semchuk KM, Olenchock SA, Senthilselvan A, eds. Agricultural Health and Safety: Workplace, Environment, Sustainability (suppl). Boca Raton (Fla): CRC Press; 1995, pp 213–216

16. US Dept of Labor. Workplace Injuries and Illnesses in 1996. Washington (DC): Bureau of Labor Statistics; 1997

17. Meister JS: The health of migrant farm workers. Occup Med 1991; 6:503–518

18. Mines R, Gabbard S, Steirman A. A Profile of US Farm Workers: Demographics, Household Composition, Income, and Use of Services. Washington (DC): US Dept of Labor, Office of the Assistant Secretary for Policy; 1997

19. Rosenberg HR, Gabbard SM, Alderete E, Mines R: California Findings from the National Agricultural Workers Survey: A Demographic and Employment Profile of Perishable Crop Farm Workers. Washington (DC): US Dept of Labor; 1993

20. Gunderson P, Gerberich S, Gibson R, Adlis S, Carr P, Erdman A, et al. Injury surveillance in agriculture. Am J Ind Med 1990; 18:169–178

21. Rossignol M. Completeness of provincial workers' compensation files to identify fatal occupational injuries. Can J Public Health 1994; 85:244–247

22. Russell J, Conroy C. Representativeness of deaths identified through the injury-at-work item on the death certificate: implications for surveillance. Am J Public Health 1991; 81:1613–1618

23. Brison RJ, Pickett CWL. Nonfatal farm injuries in eastern Ontario: a retrospective survey. Accid Anal Prev 1991; 23:585–594

24. Pratt DS, Marvel LH, Darrow D, Stallones L, May JJ, Jenkins P. The dangers of dairy farming: the injury experience of 600 workers followed for two years. Am J Ind Med 1992; 21:637–650

25. Zhou C, Roseman J. Agricultural injuries among a population-based sample of farm operators in Alabama. Am J Ind Med 1994; 25:385–402

26. Brackbill RM, Cameron LL, Behrens V. Prevalence of chronic diseases and impairments among US farmers, 1986–1990. Am J Epidemiol 1994; 139:1055–1065

27. Stueland D, Mickel SH, Cleveland DA, Rothfusz RR, Zoch T, Stamas P Jr. The relationship of farm residency status to demographic and service characteristics of agricultural injury victims in central Wisconsin. J Rural Health 1995; 11:98–105

28. Beaumont JJ, Goldsmith DF, Morrin LA, Schenker MB. Mortality in agricultural workers after compensation claims for respiratory disease, pesticide illness, and injury. J Occup Environ Med 1995; 37:160–169

29. Layde PM, Nordstrom DL, Stueland D, Brand L, Olson KA. Machine-related occupational injuries in farm residents. Ann Epidemiol 1995; 5:419–426

30. Flotre M. High-pressure injection injuries of the hand. Am Fam Phys 1992; 45:2230–2234

31. Centers for Disease Control and Prevention (CDC). Eye injuries to agricultural workers – Minnesota, 1992–1993. MMWR Morb Mortal Wkly Rep 1995; 44:364–367

32. CDC. Farm-related tractor fatalities – Kentucky 1994. MMWR Morb Mortal Wkly Rep 1995; 44:481–485

33. Thelin A. Epilogue: agricultural, occupational and environmental health policy strategies for the future. Am J Ind Med 1990; 18:523–526

34. Kelsey JW, Mey JJ, Jenkins PL. Farm tractors and the use of seat belts and roll-over protective structures. Am J Ind Med 1996; 30:447–456

35. Von Essen SG, Donham KJ. Respiratory diseases related to work in agriculture. In: Langley RL, McLymore RL, Meggs WJ, Roberson GT, eds. Safety and Health in Agriculture, Forestry and Fisheries. Rockville (Md): Government Institutes, Inc; 1997, pp 353–384

36. Malmberg P, Palmgren U, Rask-Andersen A. Relationship between symptoms and exposure to mold dust in Swedish farmers. Am J Ind Med 1986; 10:316–317

37. McCurdy SA, Ferguson TJ, Goldsmith DF, Parker JE, Schenker MB. Respiratory health of California rice farmers. Am J Respir Crit Care Med 1996; 153:1553–1559

38. Von Essen S, Robbins RA, Thompson AB, Rennard SI. Organic dust toxic syndrome: an acute febrile reaction to organic dust exposure distinct from hypersensitivity pneumonitis. Clin Toxicol 1990; 28:389–420

39. Fink JN. Hypersensitivity pneumonitis. Clin Chest Med 1992; 13:303–309

40. Mönkäre S, Haahtela T. Farmer's lung: a 5-year follow-up of eighty-six patients. Clin Allergy 1987; 17:143–151

41. Barbee RA, Callies Q, Dickie HA, Rankin J. The long-term prognosis in farmer's lung. Am Rev Respir Dis 1968; 97:223–231

42. DoPico GA, Reddan WG, Anderson S, Flaherty D, Smalley E. Epidemiologic study of clinical and physiologic parameters in grain handlers of the northern United States. Am Rev Respir Dis 1984; 130:759–765

43. Jorna THJM, Borm PJA, Valks J, Houba R, Wouters EFM. Respiratory symptoms and lung function in animal feed workers. Chest 1994; 106:1050–1055

44. Schwartz DA, Donham KJ, Olenchock SA, Popendorf WJ, Van Fossen DS, Burmeister LF, Thorne PS, Yagle SJ, Burmeister LF, Olenchock SA, Watt JL et al. Determinants of longitudinal changes in spirometric function among swine confinement operators and farmers. Am J Respir Crit Care Med 1995; 151:47–53

45. Von Essen S. Bronchitis in agricultural workers. Semin Respir Med 1993; 14:60–69

46. Von Essen SG, Thompson AB, Robbins RA, Jones KK, Dobry CA, Rennard SI. Lower respiratory tract inflammation in grain farmers. Am J Ind Med 1990; 17:75–76

47. Larsson KA, Eklund AG, Hansson LO, Isaksson BM, Malmberg PO. Swine dust causes intense airways inflammation in healthy subjects. Am J Respir Crit Care Med 1994; 150:973–977

48. Donham KJ, Reynolds SJ, Whitten P, Merchant J, Burmeister L, Popendorf WJ. Respiratory dysfunction in swine production facility workers: dose-response relationships of environmental exposures and pulmonary function. Am J Ind Med 1995; 27:405–418

49. Zejda JE, Dosman JA. Respiratory disorders in agriculture. Tuber Lung Dis 1993; 74:74–86

50. Senthilselvan A, Chen Y, Dosman JA. Predictors of asthma and wheezing in adults. Grain farming, sex and smoking. Am Rev Respir Dis 1993; 148:667–670

51. May JJ. Agriculture. In: Harber P, Schenker MB, Balmes JR, eds. Occupational and Environmental Respiratory Disease. St Louis (Mo): Mosby; 1996, pp 188–200

52. Update. NIOSH Warns: Manure Pits Continue to Claim Lives. Lexington (Ky): National Institute for Occupational Safety and Health; July 6, 1993

53. Update. NIOSH Warns Farmers of Deadly Risk of Grain Suffocation. Lexington (Ky): National Institute for Occupational Safety and Health; April 28, 1993

54. Senthilselvan A, Zhang Y, Dosman JA, Barber EM, Holfeld LE, Kirychuk SP, et al. Positive human health effects of dust suppression with canola oil in swine barns. Am J Respir Crit Care Med 1997; 156(pt 1):410–417

55. Mueller-Wening DH, Repp H. Investigation on the protective value of breathing masks in farmer's lung using an inhalation provocation test. Chest 1989; 95:100–105

56. Prather TG. Personal protective equipment in agriculture, forestry, and fisheries. In: Langley RL, McLymore RL, Meggs WJ, Roberson GT, eds. Safety and Health in Agriculture, Forestry and Fisheries. Rockville (Md): Government Institutes, Inc; 1997, pp 181–195

57. Siebens D. Noise and hearing loss in agriculture, forestry, and fisheries. In: Langley RL, McLymore RL, Meggs WJ, Roberson GT, eds. Safety and Health in Agriculture, Forestry and Fisheries. Rockville (Md): Government Institutes, Inc; 1997, pp 59–65

58. Plakke B, Dare E. Occupational hearing loss in farmers. Public Health Rep 1992; 107:188–192

59. Kristensen S, Gimsing S. Occupational hearing impairment in pig breeders. Scand Audiol 1988; 17:191–192

60. Broste SK, Hansen DA, Strand RL, Stueland DT. Hearing loss among high school students. Am J Public Health 1989; 79:619–622

61. Blair A, Zahm SH. Cancer among farmers. Occup Med 1991; 6:335–354

62. Weisenburger DD. Human health effects of agrichemical use. Hum Pathol 1993; 24:571–576

63. Zahm SH, Weisenburger DD, Babbitt PA, Saal RC, Vaught JB, Cantor KP, et al. A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in eastern Nebraska. Epidemiology 1990; 1:344–356

64. Meggs W, Langley RL. Chemical hazards of farming. In: Langley RL, McLymore RL, Meggs WJ, Roberson GT, eds. Safety and Health in Agriculture, Forestry and Fisheries. Rockville (Md): Government Institutes, Inc; 1997. pp 249–265

65. Rosenstock L, Kiefer M, Daniell W, McConnell R, Claypoole K. Chronic central nervous system effects of acute organophosphate pesticide intoxication. The Pesticide Health Effects Study Group. Lancet 1991; 338:223–227

66. Weinbaum Z, Samuels SJ, Schenker MB: Risk factors for occupational illnesses associated with the use of paraquat (1,1′-dimethyl-4,4′-bipyridylium dichloride) in California. Arch Environ Health 1995; 50:341–348

67. Helmers S, Top RH, Knapp LW. Ammonia injuries in agriculture. J Iowa Med Soc 1971; 61:271–280

68. Leduc D, Gris P, Lheureux P, Gevenois PA, De Vuyst PD, Yernault JC. Acute and long term respiratory damage following inhalation of ammonia. Thorax 1992; 47:755–757

69. Pesticide Use Reporting: An Overview of California's Unique Full Reporting System. Sacramento: California Environmental Protection Agency, Dept of Pesticide Regulation; 1995

70. Pesticide Use Report, Annual 1995, Indexed by Chemical. Sacramento: California Environmental Protection Agency, Dept of Pesticide Regulation; 1996

71. Overview of the California Pesticide Illness Surveillance Program, 1995. Sacramento: California Environmental Protection Agency, Dept of Pesticide Regulation; 1997

72. Weinbaum Z, Schenker MB, O'Malley MA, Gold EB, Samuels SJ. Determinants of disability in illnesses related to agricultural use of organophosphates (OPs) in California. Am J Ind Med 1995; 28:257–274

73. Burke WA. Skin diseases in farmers. In: Langley RL, McLymore RL, Meggs WJ, Roberson GT, eds. Safety and Health in Agriculture, Forestry and Fisheries. Rockville (Md): Government Institutes, Inc; 1997, pp 321–352

74. Langley RL, Morrow MWE. Zoonotic hazards in humans in agriculture, forestry, and fisheries. In: Langley RL, McLymore RL, Meggs WJ, Roberson GT, eds. Safety and Health in Agriculture, Forestry and Fisheries. Rockville (Md): Government Institutes, Inc; 1997, pp 127–141

75. Donham KJ. Zoonotic diseases of occupational significance in agriculture: a review. Int J Zoon 1985; 12:163–191

76. Keusch GT, Hamer D, Joe A, Kelley M, Griffiths J, Ward H. Cryptosporidia—who is at risk? Schweiz Med Wochenschr 1995; 125:899–908

77. Ruppanner R, Schwabe CW. Early records of hydatid disease in California. Am J Trop Med Hyg 1973; 22:485–492

78. Flanagan PG, Westmoreland D, Stallard N, Stokes IM, Evans J. Ovine chlamydiosis in pregnancy. Br J Obstet Gynecol 1996; 103:382–385

79. Arends JP, Zanen HC. Meningitis caused by *Streptococcus suis* in humans. Rev Infect Dis 1988; 10:131–137

80. Brown WD. Heat and cold in farm workers. Occup Med 1991; 6:371–389

81. Gun RT, Budd GM. Effects of thermal, personal and behavioral factors on the physiological strain, thermal comfort and productivity of Australian shearers in hot weather. Ergonomics 1995; 38:1368–1384

82. Occupational Injuries and Illnesses Survey, California, 1995. San Francisco: California Dept of Industrial Relations, Division of Labor Statistics and Research; 1997

83. Holness D, Nethercott J. What actually happens to the farmers? clinical results of a follow-up study of hog confinement farmers. In: McDuffie HH, Dosman JA, Semchuk KM, Olenchock SA, Senthilselvan A, eds. Agricultural Health and Safety: Workplace, Environment, Sustainability. Boca Raton (Fla): CRC Press; 1995, pp 49–52

84. May JJ. A study of osteoarthritis of the knee and hip in dairy farmers. NIOSH Symposium on Efforts to Prevent Injury and Disease Among Agricultural Workers. Lexington (Ky): National Institute for Occupational Safety and Health; 1994

85. Palmer KT: Musculoskeletal problems in the tomato growing industry: "tomato trainer's shoulder"? Occup Med (Oxf) 1996; 46:428–431

86. Sakakibara H, Miyao M, Kondo T, Yamada S: Overhead work and shoulder-neck pain in orchard farmers harvesting pears and apples. Ergonomics 1995; 38:700–706

87. Miles JA, Steinke WE. Citrus workers resist ergonomic modifications to picking ladder. J Agricult Safety Health 1996; 2:7–15

88. McKnight RH, Levine EJ, Rodgers GC Jr. Detection of green tobacco sickness in a regional poison center. Vet Hum Toxicol 1994; 36:505–510

Epitomes

Important Advances in Dermatology

Dermatology

Seth L. Matarasso, MD, Section Editor

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in dermatology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, as to both scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in dermatology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Dermatology of the California Medical Association, and the summaries were prepared under the direction of Dr Matarasso and the Panel.

Psoriasis Therapy Update

THE THERAPY OF PSORIASIS can be subdivided into 3 categories: topical therapies, phototherapies, and systemic therapies.

Topical Therapies

The history of topical steroid therapy in dermatology has featured the synthesis of increasingly potent preparations. However, local side effects (steroid atrophy, folliculitis, opportunistic skin infections, etc.) and the potential for absorption and suppression of the hypothalamic-pituitary-adrenal axis limit their use. In addition, loss of efficacy over time can occur. Thus, nonsteroidal alternatives for the topical treatment of psoriasis are desirable. Recently, a vitamin D3 analog, calcipotriene, has been approved for the topical treatment of psoriasis. Calcipotriene works by decreasing epidermal proliferation and enhancing differentiation; it may have immunomodulatory properties as well. The potency of calcipotriene ointment approximates that of topical fluocinonide without the potential hazards of topical steroid treatment or the problem of tachyphylaxis. Unfortunately, compared to topical steroids, its onset of action is rather slow (4-6 weeks) and cutaneous irritation may occur. Thus, initial combination treatment with a topical steroid and calcipotriene allows for more rapid onset of improvement with less irritation. Later, the patient may be switched to calcipotriene treatment alone. Other vitamin D3 analogs are in clinical trials, as are topical tacrolimus (an immunosuppressant drug) and various ascomycin derivatives (which have antiinflamatory activities). Tazarotene, a topical retinoid, also has been approved for the topical treatment of psoriasis, although cutaneous irritation is quite common, and the marketed preparation is extremely expensive.

Phototherapies

Natural sunlight (heliotherapy) is a cheap and effective way of treating psoriasis, and most patients notice remission during the summer. Artificial sources of ultraviolet B irradiation (UVB) are also helpful. Patients can purchase a UVB light unit for home use, but the frequency and intensity of therapy should be monitored by the physician at least quarterly. Narrow-band UVB is a new form of UVB therapy that may offer some advantages over broadband UVB treatment. Photochemotherapy (PUVA), a combination of oral 8-methoxypsoralen followed by ultraviolet A (UVA) exposure, is highly effective in the treatment of psoriasis. However, cutaneous carcinogenesis is a major concern after long term use. With any form of phototherapy, a sunscreen should be applied to uninvolved areas to decrease the risk of skin cancer.

Systemic Therapies

Methotrexate (an antimitotic and antiinflammatory agent) and acetretin (an oral retinoid) are the most commonly used systemic therapies for psoriasis. Both drugs have important short- and long-term side effects and should be prescribed only by physicians familiar with their use. Recent studies have suggested that gastrointestinal side effects from methotrexate may be alleviated by ingestion of folic acid. Although periodic liver function tests are routinely performed on patients undergoing methotrexate therapy, the results may remain normal in the face of underlying hepatic damage, which can be reliably assessed only by liver biopsy. Acetretin and its parent drug, etretinate, are known teratogens. Female patients receiving acetretin should use two forms of contraception during the treatment period and for at least 3 years thereafter. Hypertryglyceridemia is common, especially in older patients. Myriad other adverse effects associated with acetretin therapy should be reviewed

with the patient by the prescribing physician. Cyclosporine is effective in the treatment of psoriasis, but hypertension and decreased renal function are common sequelae; thus, only patients with severe disease warrant its administration. As with methotrexate, a prompt and often severe rebound can occur after treatment is discontinued. Systemic administration of corticosteroids should never be used in treatment, except in the rare patient with severe, life-threatening psoriasis.

Combination Therapies

Combination therapy permits the use of lower doses of the individual components, thus decreasing their individual toxicities. Combination therapy may include the concurrent use of a topical preparation, such as calcipotriene ointment, with either a phototherapy or systemic therapy, or the use of a systemic agent, such as acetretin, with a phototherapy. For most patients with moderate to severe psoriasis, combination therapy is more effective and less hazardous than monotherapy.

BRUCE H. THIERS, MD
Charleston, South Carolina

REFERENCES

Hepburn DJ, Aeling JL, Weston WL. A reappraisal of topical steroid potency. Pediatr Dermatol 1996; 13:239–245

Lebwohl M, Siskin SB, Epinette W, et al. A multicenter trial of calcipotriene ointment and halobetasol ointment compared with either agent alone for the treatment of psoriasis. J Am Acad Dermatol 1996; 35:268–269

Orfanos CE, Zouboulis CC, Almond-Roesler B, et al. Current use and future potential role of retinoids in dermatology. Drugs 1997; 53:358–388

The Pathogenesis of Kaposi's Sarcoma

KAPOSI'S SARCOMA (KS) HAS received immense attention since 1981 when it was first recognized as a major manifestation of the Acquired Immune Deficiency Syndrome (AIDS). Four forms have been described: an indolent, endemic form seen most commonly in older Mediterranean men; a second form seen in tropical Africa commonly affecting children; an "iatrogenic" form that occurs in individuals receiving immunosuppressive therapy such as organ transplant recipients; and the form associated with HIV infection. Skin lesions are similar in all groups and all appear similar histologically. Vascular endothelial cells are thought to be the cell of origin of KS on the basis of morphology, presence of vascular spaces, ultrastructural appearance, and the expression of various endothelial markers.

The true nature of KS is a subject of intense study. Whether KS is a clonally derived malignancy or a proliferation of spindle cells in response to local cytokines has been a subject of controversy. High local levels of cytokines including interleukin 6 (IL-6), basic fibroblast growth factor (bFGF), tumor necrosis factor α (TNF-α), interferon γ and vascular endothelial growth factor (vEGF) have been shown to be present in KS lesions. Interleukin-6 is produced by KS spindle cells themselves and exogenous IL-6 has been shown to enhance the proliferation of KS cells in culture. Other features that favor a proliferative rather than truly neoplastic process include the fact that there are often many lesions that develop simultaneously without a characteristic primary lesion and the absence of a tendency to spread regionally to local lymph nodes. Furthermore, lesions often resolve when the patient's immunocompetence is reconstituted. On the other hand, a recent article demonstrated clonality of KS lesions with identical genetic sequences in different KS lesions in the same patient. This does not necessarily prove that KS develops from a primary lesion and spreads throughout the body, however.

An infectious etiology for KS has been sought for over 3 decades. In 1994 Chang and Moore discovered herpes-like DNA sequences in KS tissues from patients with AIDS. These sequences were not identified in tissues from normal hosts, lymph nodes, peripheral lymphocytes infected with Epstein Barr virus (EBV), DNA extracted from other vascular tumors, or other tissues involved with AIDS opportunistic infections. These DNA sequences are partially homologous to gene segments of γ-herpesvirinae such as *Herpesvirus saimiri* and EBV. This novel herpesvirus associated with KS was thus classified as a γ-herpesvirinae and called Kaposi's sarcoma-associated herpesvirus (KSHV) or Human Herpesvirus-8 (HHV-8).

Since HHV-8 was discovered, researchers have sought to prove that the virus is truly the cause of KS and not simply a co-factor. Three bodies of evidence suggest causality. First, HHV-8 is present in all types of KS and is present in virtually all samples tested to date. Second, serologic studies show that the prevalence of HHV-8 infection in various geographic and risk-group populations parallels the incidence of KS in these populations. Third, both polymerase chain reaction (PCR)-based detection of HHV-8 DNA in peripheral blood and antibody seroconversion studies show that HHV-8 infection occurs before the development of KS and is highly predictive of its development.

Current research aims to define the role of HHV-8 in initiating the pathogenesis of KS lesions. Several potential oncogenes have been identified that allow the virus to avoid antiviral responses such as cell-cycle arrest, apoptosis and enhanced cell-mediated immunity, any of which could lead to abnormal cell proliferation.

The current treatment options for all forms of widespread or systemic KS include cytotoxic drugs (bleomycin, vinca-alkaloids, anthracyclines and taxol), systemic interferon and radiotherapy. Overall, conventional chemotherapy and radiation are only partially effective and have significant adverse effects. Novel approaches that take into account the recent discoveries of molecular factors that produce KS lesions are already in development. Drugs that diminish angiogenesis in KS have been shown to be at least partially effective in preliminary studies. For example, thalidomide, a drug that blocks angiogenesis in developing limb buds, has been reported to induce regression of KS lesions in some

patients. Antiviral agents that with activity against HHV-8 such as foscarnet, ganciclovir and acyclovir are also currently being investigated and preliminary results indicate that foscarnet may cause remission of some KS lesions. Furthermore, KS lesions in HIV-positive individuals often resolve after initiation of treatment with Highly Active Antiretroviral Therapy (HAART) that includes 2 nucleoside reverse transcriptase inhibitors and a protease inhibitor. Although HAART may have some antiviral activity against HHV-8, it is likely that the effect is related to improvement in the patient's immunity. This is analogous to the regression seen in KS that develops in transplant patients when immunosuppression is stopped.

Thus, the cause and pathogenesis of KS are becoming clearer. As a consequence, new and more effective treatments are being developed.

SARAH RODMAN, MS IV
CLAY J. COCKERELL, MD
Dallas, Texas

REFERENCES

Boshoff C, Weiss RA. Aetiology of Kaposi's sarcoma: current understanding and implications for therapy. Mol Med Today 1997; 3:488–494

Greenblatt, RM. Kaposi's sarcoma and human herpesvirus-8. Infect Dis Clin N Am 1998; 12:63–82

Dermatoses of Pregnancy

MANY CUTANEOUS CHANGES occur during pregnancy, including pigmentary (linea nigra, melasma, darkening of nevi), glandular (increased eccrine and sebaceous gland function, decreased apocrine function), and vascular (spider hemangiomas, palmar erythema, pyogenic granulomas). About 1.6% of women will develop pruritus during pregnancy. Five dermatoses are specific to pregnancy: pruritic urticarial papules and plaques of pregnancy (PUPPP), herpes gestationis (HG), cholestasis of pregnancy (pruritus gravidarum), impetigo herpetiformis and linear IgM dermatosis of pregnancy (LMDP). Some authors prefer the term "polymorphic eruption of pregnancy" (PEP) to encompass PUPPP, prurigo of pregnancy and pruritic folliculitis of pregnancy.

PUPPP occurs in approximately 1/240 pregnancies, mainly in primigravidas in their third trimester, and is characterized by intensely pruritic urticarial papules and plaques. The lesions typically begin in the striae on the lower abdomen, sparing the periumbilical area, and later spread to involve the breasts, back, and extremities. Pinpoint vesicles may be present, but bullae should raise the clinical suspicion for HG. The latter is confirmed by direct immunofluorescence testing (which is negative in PUPPP). There is no associated fetal morbidity or mortality, but the pruritus is often intractable. The eruption resolves spontaneously shortly after delivery. Although the etiology is unknown, it has been postulated to be related to abdominal distention, and cases involving twin and triplet pregnancies are common. Treatment includes topical steroids and oral antihistamines, but oral corticosteroids may be required in severe cases.

Prurigo of pregnancy may be a distinct entity, or it may represent an unusual variant of PUPPP. It occurs in approximately 1/300 women, with an onset in the 25th–30th week of pregnancy. Itchy, grouped, excoriated papules develop primarily on the extensor surfaces of the extremities in patients with an atopic diathesis. Treatment is symptomatic, and there is no associated fetal morbidity or mortality.

Pruritic folliculitis of pregnancy is most likely a form of acne/folliculitis that occurs in pregnancy due to hormonal alterations. Patients in their 4th–9th month of pregnancy develop generalized, excoriated follicular papules and sterile pustules that resolve shortly after delivery. Mid-potency topical corticosteroids and oral antihistamines have been used but without significant benefit in most patients.

HG occurs in 1/7000 pregnancies. Patients develop severely pruritic, urticarial plaques and tense bullae on the trunk and extremities. The umbilicus is commonly involved. The disease usually requires systemic corticosteroids and may persist for months or years after delivery. A postpartum flare occurs in 75% of patients, and approximately 25% flare with oral contraceptives or menses. About 5% of patients' newborns will have transient blisters; there is an increased risk of prematurity and a tendency for small-for-gestational-age babies. The disease commonly recurs in subsequent pregnancies. In contrast to PUPPP, direct immunofluorescence is positive, revealing linear C3 along the basement membrane zone in 100% of patients.

The incidence of cholestasis of pregnancy varies widely in different countries and ethnic groups. The incidence in North America, for example, is approximately 1/1293, while in Chile and Scandanavia it occurs in 3% to 14% of the population. In this disorder, patients develop severe generalized pruritus, in the absence of primary lesions. The degree of pruritus directly correlates with the level of serum bile acids, which is often markedly elevated. Symptoms begin in the late 2nd to early 3rd trimester and usually resolve within 48 hours of delivery. There is often mild elevation of liver function tests, but if the bilirubin is normal, the disease is referred to as "pruritus gravidarum." Treatment has included phenobarbital, cholestyramine, and ion exchange resin, often without significant benefit. The disease may recur in subsequent pregnancies.

Impetigo herpetiformis has been infrequently reported in the literature. Patients in their third trimester develop generalized pustules on a background of erythema and scaling. The eruption may be accompanied by fever, nausea and vomiting, and leukocytosis. If the patient develops hypocalcemia, she may develop tetany, seizures, and delirium. Because of placental insufficiency, there is an increased risk of stillbirth. The disease remits promptly after delivery. Because of its clinical resemblance to pustular psoriasis and the extremely low levels of skin-derived antileucoproteinase found in patients, this disease is felt to represent a variant of pustular psoriasis.

LMDP is also rarely reported. It occurs in the 3rd trimester as pruritic, red, follicular papules on the trunk

and extremities. The eruption resolves within weeks after delivery. A biopsy for direct immunofluorescence reveals linear IgM at the basement membrane zone. Some patients with a similar presentation may have circulating IgM antibodies detected on indirect immunofluorescence testing.

In summary, a number of eruptions occur during pregnancy that have characteristic clinical, histopathological, and laboratory findings. It is important for the clinician to be familiar with these, not only for treatment if it is necessary, but also in order to discuss with the patient the risk of recurrence in subsequent pregnancy and any risk to the fetus or newborn.

LISA M. COHEN, MD
Boston, Massachusetts

REFERENCES

Vaughan Jones SA, Dunnill MGS, Black MM. Pruritic urticarial papules and plaques of pregnancy (polymorphic eruption of pregnancy): two unusual cases. Br J Dermatol 1996; 135:102–105

Black MM. Progress and new directions in the investigation of the specific dermatoses of pregnancy. Keio J Med 1997; 46:40–41

Kuijpers ALA, Schalkwijk J, Rulo HFC, et al. Extremely low levels of epidermal-derived antileucoproteinase/elafin in a patient with impetigo herpetiformis. Br J Dermatol 1997; 137:123–129

Roger D, Vaillant L, Fignon A et al. Specific pruritic diseases of pregnancy. A prospective study of 3192 pregnant women. Arch Dermatol 1994; 130:734–739

Evaluation and Treatment of Onychomycosis

DISTAL SUBUNGUAL ONYCHOMYCOSIS, the most common type of nail fungus, may affect as much as 10–12% of the population. In the geriatric age group, this figure may reach as high as 50%. Since older persons are one of the fastest growing segments of our society, tinea unguium becomes a major health problem that causes disability and has a major serious impact on quality of life. Fortunately, in the last several years, 3 safe and effective oral antifungals have become available for use. The likelihood for a cure is good, but there is approxiamtely a 15% recurrence rate.

Before starting therapy, it is essential that the diagnosis of onychomycosis be confirmed. Since fungal nail infections comprise only 50% of dystrophic nails, it follows logically that other conditions make up the 50% balance. Psoriasis, lichen planus, nail cosmetic sensitivity, and many other disorders also enter into the differential diagnosis. The most commonly used diagnostic tests are the traditional KOH wet mount and culture. If either one or both of these investigations is positive, the diagnosis is proved and therapy may be commenced. Since as much as 30% of these mycologic tests may be negative even in the presence of onychomycosis, two additional steps may become necessary. Histopathology of nail clippings with PAS staining is an effective and noninvasive method to identify fungi and is accurate well over 90% of the time with the possible exception of very early cases. In the latter situation, the nail plate has not yet been invaded by the fungi and, therefore, hyphae may not be present but that is uncommon. Finally, if all else fails to provide a diagnosis, a nail bed biopsy could be performed which, if eliminating fungus as a causative factor, may then provide a specific diagnosis.

The 3 new oral antifungal agents that are currently available for the treatment of distal subungual onychomycosis are itraconazole (Sporanox), terbinafine (Lamisil), and fluconazole (Diflucan). These drugs are major breakthroughs for two reasons. First, all 3 reach the nail plate rapidly, within 7–21 days. The old standby, griseofulvin, requires 6 months to reach the distal plate of a finger and 12 months or more to reach the same site in a toe because matrix incorporation is required. The new drugs reach the nail quickly because they diffuse upward from the nail bed and do not require matrix incorporation. Second, whereas griseofulvin disappears from the nail as early as 2 weeks after treatment is stopped, the new ones remain active in the nail for several months after therapy is discontinued.

Itraconazole was the first product to be approved by the FDA. It is a triazole that is lipophilic, has high protein binding, and strong tissue affinity. Itraconazole may be given on a daily basis at 2 capsules (100 mg each) per day after meals for 2 months for fingernails and three months for toenails. The new "pulse" regimen may also be employed and has become a popular form of treatment. It requires 2 capsules twice daily for 1 week on and 3 weeks off. Two pulses are needed for fingernails and 3 for toenails. Drug interactions leading to adverse sequelae such as heart problems can occur with itraconazole, and the following are contraindicated: cisapride, simvastatin, lovastatin, astemazole, triazolam, and midazolam.

The second product to be approved by the FDA was terbinafine. It is an allyl amine that is also lipophilic. It is given in a dosage of one 250-mg tablet daily for 6 weeks for fingernails and 3 months for toenails. There are no contraindicated drug interactions because terbinafine does not interact with the cytochrome P450 system to the extent that azoles do.

The last of the triumvirate, fluconazole, has not yet been approved by the FDA for the treatment of onychomycosis, although it is available for some systemic fungal infections. It, like itraconazole, is a triazole but it is hydrophilic and not lipophilic. The dosage schedule is 150–300 mg once per week, that is, on an intermittent basis. The treatment duration varies but most cases require 5–7 months to clear toenails, at a cost of $400–$500. Fingernails require less time, and as a result treatment cost is also less. Fluconazole is available in 50-, 100-, and 200- mg tablets. It is impacted by the cytochrome P450 system and therefore has many drug interactions with which the treating physician must become familiar before prescribing. To date, none has been labeled as contraindicated.

Medical surveillance for patients undergoing treatment should include baseline complete blood count and liver function tests, which should be repeated approximately every 6 weeks.

In summary, we are now in a new era in the treatment of onychomycosis. It behooves the medical community to revisit this important, though fortunately not life threatening, disease that is much more than a cosmetic problem.

RICHARD K. SCHER, MD
New York, New York

REFERENCES

Cohen JL, Gupta AK, Scher RK, et al. The nail and fungus infection. In: Elewski BE, editor. Cutaneous fungal infections. 2nd ed. Oxford: Blackwell Science, Inc.; 1998, pp 119–153

Elewski BE, Charif MA, Daniel CR III. Onychomycosis. In: Scher RK, Daniel CR III, editors. Nails: therapy, diagnosis, surgery. 2nd ed. Philadelphia: W.B. Saunders Co.; 1997, pp 151–162

Public Awareness of the Threat of Melanoma and Performance of Skin Self-Examination

THE DETECTION AND TREATMENT of melanoma early in its course is critical because survival in persons with early or thin melanoma (equal to or less than 0.75 mm) approaches 100% and falls to 55% for more advanced or thick tumors, greater than 3.00 mm. Skin self-examination for melanoma could enhance its early detection and could reduce mortality from melanoma by 63%. Currently, most melanomas are discovered by patients and their family members. Thus, regular skin self-examination or skin examination with the aid of a partner to see difficult areas, e.g. back of legs, back of head, can increase the number of patients who seek medical care early.

In the United States, melanoma incidence and mortality continue to rise each decade. The incidence of melanoma is estimated to be approximately 10 per 100,000, and this may be doubling worldwide every 10–15 years. The lifetime risk is estimated to be 1 in 600 for someone born in 1960 and 1 in 75 for someone born in the year 2000. While Scotland and Australia have experienced a reduction in melanoma mortality rates following broad public educational campaigns, the United States has not yet experienced such a decline. The recently enhanced public awareness of melanoma and acceptance of skin self-examination brings more worried patients into the offices of all physicians, thus increasing case finding by all health care professionals. The desired decline in US mortality rates could be attained by monthly skin self-examination performed by the at-risk population and proficiency of health care professionals in early detection of melanoma with referral of clinically suspicious cases to the dermatologist for biopsy and treatment. All health care professionals should become proficient in identifying those at high risk of developing a melanoma, informing patients of their individual risk, and counseling patients about how to perform skin self-examination using the ABCD rule (Asymmetry of the shape of the mole, Border irregularity, Color variation over the surface of the mole, and Diameter greater than 6 mm). Those whose advice may likely be sought, primary care physicians, need sufficient training themselves in identifying clinically suspicious lesions.

JUNE K. ROBINSON, MD
Chicago, Illinois

REFERENCES

Berwick M, Begg CB, Fine JA. Screening for cutaneous melanoma by skin self-examination. J Natl Cancer Inst 1996; 88:17–23

Robinson JK, Rigel DS, Amonette RA. What promotes skin self-examination? J Am Acad Dermatol 1998; 39:752–757

Rigel DS, Friedman RJ, Kopf AW. The incidence of malignant melanoma in the United States: issues as we approach the 21st century. J Am Acad Dermatol 1996; 34:839–47

Rigel DS, Friedman RJ, Kopf AW, Robinson JK, Amonette RA. Melanoma incidence: if it quacks like a duck. Arch Dermatol 1997; 133:656–659

HIV Related Skin Diseases Clear with Combination Therapy

FROM THE BEGINNING of the AIDS epidemic in 1981, the skin was observed to be a key barometer of immunodeficiency. Diseases such as seborrheic dermatitis and onychomycosis appear with modest drops in the CD4 count. Kaposi's sarcoma, oral candidiasis and herpes zoster appear with progressive loss of CD4 cells and, finally, oral hairy leukoplakia, molluscum contagiosum, eosinophilic folliculitis and resistant herpes simplex are seen with profound levels of immunodeficiency.

The association of herpes zoster, oral candidiasis, oral hairy leukoplakia and molluscum contagiosum is so profound that these cutaneous conditions were used as signs of disease progression in early clinical trials of antiviral medications. Although they are not as precise as the CD4 count in measuring the level of immunodeficiency and are certainly not as useful as the viral load in measuring the rate of disease progression, they are of great value in underdeveloped countries where expensive laboratory tests are not available.

Furthermore, these conditions are so strongly tied to HIV infection that there have now been a number of lawsuits filed against physicians who diagnosed herpes zoster in young people and did not discuss with them the wisdom of having an HIV test performed.

The introduction of combined antiretroviral therapy showed that if the physician was successful in getting the patient's viral load below the level of detection, the patient's disease did not progress, the CD4 count began to rise, and his or her general well-being improved. At the same time, patients with Kaposi's sarcoma showed almost immediate arrest in the rate of progression of their disease with ongoing improvement if the viral load remained below the level of detection. Eosinophilic folliculitis may initially flare with aggressive therapy, but also clears as the CD4 count rises above 100. Molluscum contagiosum becomes easily manageable and candida and oral hairy leukoplakia clear.

Thus in this second phase of the AIDS epidemic, the treatment of choice for most HIV associated skin diseases, including Kaposi's sarcoma, is aggressive antiretroviral

therapy and maintenance of the viral load below the level of detection. If the viral load cannpt be reduced below the level of detection, the patient will become resistant to the drugs being used and the disease will recur and progress.

MARCUS A. CONANT, MD
San Francisco, California

REFERENCES

Carpenter CC, Fischl MA, Jammer SM, et al. Antiretroviral therapy for HIV infection. JAMA 1998; 280:78–86

Pabella FJ, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodefiency virus infection. N Engl J Med 1998; 338:853–860

The Role of Clostridium Botulinum: A Neurotoxin in Clinical Dermatology

CLOSTRIDIUM BOTULINUM PRODUCES seven (A–G) serologically distinct neurotoxins, and type A (Botox, Allergan, Inc., Irvine, CA) is the most potent. Upon exposure to striated muscle, it prevents release of acetylcholine from the presynaptic neuron at the neuromuscular junction. The effect of this inhibition is a chemical denervation resulting in flaccid muscle paralysis. This paralytic effect has historically been intimately associated with lethal systemic botulism toxicity. In 1973 small amounts of purified intramuscular Botox were found to be therapeutic for numerous neuromuscular disorders involving the periocular anatomy. Serendipitously it was realized that with paresis of the underlying hyperkinetic muscles, many wrinkles were effaced without altering cutaneous sensation. Since this initial finding, there has been an exponential surge in the understanding and use of botulinum A exotoxin.

As a sole or as an ancillary procedure, Botox has extraordinary utility in the treatment of the stigmata of facial aging. Injection of 30–40 units of Botox into the corrugator supercilii and procerus muscles paralyzes the glabellar complex and improves the deep midline furrow. Smaller amounts, 20–30 units, are required to treat the lateral fibers of the orbicularis oculi muscle that causes the crow's feet deformity. The frontalis muscle is the large forehead muscle and contraction causes pronounced horizontal creases. Injection of 50–60 units of Botox will effectively eradicate these lines. With age and hyperkinetic movement of the platysma muscle, the neck can prematurely appear senescent with horizontal rhytides and thick vertical platysma bands. Serial injections into the belly of this muscle releases the downward pull of the muscle and results in a reduction in horizontal neck lines and a sharper cervicomental angle. Additionally, there have been reports of treatment of other facial muscles inclusive of the nasalis, mentalis, and orbicularis oris muscles for facial rejuvenation.

The onset of action of Botox is between 3 to 7 days and can persist for many months. Upon muscle reanimation and reappearance of the aesthetic defect, reinjection can be performed at the patient's discretion. Clinical evidence suggests that with each subsequent treatment, there is further muscle atrophy and the duration of the effect of Botox is prolonged.

Botox can also be used synergistically with other facial rejuvenative procedures. Following facial plasty surgery, wrinkles can further be diminished with Botox. Similarly, reducing muscle contraction with Botox before resurfacing or soft tissue augmentation has been found to sustain the effects of both procedures.

In another area, axillary and palmar hyperhidrosis have long been problematic for patients, and despite many different forms of therapy, long-term improvement remains elusive. By inhibiting contraction of the eccrine gland myoepithelial cell, serial intradermal injections of Botox have resulted in a profound reduction in the amount and severity of hyperhidrosis.

The use of Botox therapeutically as well as for facial rejuvenation by paralyzing selected facial muscles has rapidly been embraced by physicians and patients alike. It is remarkably effective and safe, without permanent deleterious side effects, and therefore provides an acceptable risk-to-benefit ratio. However, more documentation and follow-up are necessary to establish standard injecting guidelines and define optimal doses and volumes. To reduce the risk of adverse sequelae such as ptosis (eyelid or eyebrow) or facial assymetry, it remains incumbent upon physicians to be familiar with both the indications for Botox and the muscular anatomy underlying facial expression. It is also prudent to inform patients about the potency and the fact that this is off-label use of the drug (the U.S. Food and Drug Administration has approved Botox for the treatment of strabismus, benign essential blepharospasm, and facial nerve disorders), as well as to advise them about alternative therapies, duration of benefit, and the potential complications.

SETH L. MATARASSO, MD
San Francisco, California

REFERENCES

Carruthers A, Carruthers J. Cosmetic uses of botulinum A exotoxin. Adv Dermatol 1997; 12:325–347

Matarasso SL, Carruthers A. Botulinum toxin: treatment for glabellar furrows. J Geriatr Dermatol 1997; 5:13–14

Bushara KO, Park DM, Jones JC, Schutta HS. Botulinum toxin—a possible new treatment for axillary hyperhidrosis. Clin Exp Dermatol 1996; 21:276–278

Disorders of Pigmentation: Global Issues of Major Cosmetic Concern

PIGMENTARY DISORDERS AFFECT billions of patients globally and cause significant cosmetic disfigurement. Although these lesions occur in all races, they are most visible in darker-skinned individuals. Even though patients experience tremendous despair regarding pigmentary imperfections, they are often not treated and patients may be told that treatments are ineffective.

Dyschromic conditions are characterized by patches of hyperpigmentation, hypopigmentation, or depigmentation. Histological studies often demonstrate a variety of changes, including defects in melanin production, melanin

deposition, melanin transfer and/or quantitative alterations in melanocytes. Common dyschromias include melasma, post-inflammatory hyperpigmentation, and vitiligo.

Melasma is a common disorder of hyperpigmentation in which typical brown or grayish brown macules appear on the face, including the cheeks, forehead, upper lip, and chin. Although the condition occurs in all racial-ethnic groups, it tends to be most common in darker-skinned individuals and it is observed most often in women.

Factors implicated in the pathology of melasma include ultraviolet radiation, oral contraceptives, pregnancy, and cosmetics. Three clinical patterns of hyperpigmentation are recognized: malar, centrofacial, and mandibular. Histological patterns of pigmentation include epidermal, dermal, and a mixed variety in which excess pigment is deposited in both the epidermis and dermis. Current therapies for melasma are predicated on the severity of clinical lesions. For patients with mild to moderate disease, monotherapies include topical 2% and 4% hydroquinone, azelaic acid, kojic acid, tretinoin, and alpha hydroxy acids. Of these, hydroquinone remains the gold standard. For patients with moderate to severe involvement, approaches using combinations of the aforementioned bleaching agents in conjunction with superficial chemical peels work best. One cannot overemphasize the importance of daily use of broad-spectrum sunscreens in treating melasma.

Post-inflammatory hyperpigmentation is characterized by macules or patches of hyperpigmentation that develop in response to cutaneous injury. Excess pigment deposition may be confined to the epidermis or occur in both the epidermis and dermis. As with melasma, post-inflammatory hyperpigmentation tends to be most severe in darker racial-ethnic groups. Pigmentary lesions occur at the site of cutaneous injury, and so may appear on any area of the body. Post-inflammatory hyperpigmentation is caused by a variety of inflammatory disorders including acne and eczematoid, papulosquamous, and vesiculo bullous conditions. If the underlying inciting disease is treated, in contrast to melasma, post-inflammatory hyperpigmentation may remain quiescent or improve with time. Most patients require some form of therapeutic intervention, however. Therapies include topical bleaching agents (see melasma). Combination therapies using topical bleaches in conjunction with superficial chemical peels may be beneficial in patients with severe disease affecting facial areas. Therapeutic response often correlates with the depth of pigment deposition, i.e. deposition in the dermis alone vs deposition in both the epidermis and dermis. Maximal results are achieved in patients with only epidermal hyperpigmentation. Significant clinical improvement can be induced in many patients with epidermal and dermal pigment deposition, however, via induction of a decrease in epidermal melanin.

Vitiligo is a common disorder of hypopigmentation affecting 1% to 2% of the population. Macules or patches of depigmentation occur in a localized, acral, acral-facial, generalized or segmental distribution. The disease has an equal incidence in all racial groups. It is most evident in darker racial-ethnic groups, however, because of of the striking contrast between depigmented and normal skin. Because of the profound cosmetic disfigurement, patients often experience severe emotional trauma. Histologically the disease is characterized by an absence of cutaneous melanocytes. Proposed theories of destruction of melanocytes include autoimmune, neural, autocytotoxic, biochemical, and viral mechanisms. Autoimmune diseases are increased in vitiligo patients. Thirty percent of patients show evidence of thyroid dysfunction. Despite advances in treatment of vitiligo, dermatologists and non-dermatologists regularly inform patients that all treatments are ineffective. These statements are mythical, fallacious, and frustrating. Treatment planning is based on the extent of cutaneous surface involvement and progression of the disease. Therapies include topical steroids, systemic steroids (for extensive, progressive disease), topical and oral photochemotherapy and immunomodulators. In addition, isolated stable lesions can be treated by a variety of surgical grafting procedures. Therapeutic reponses are enhanced in children with vitiligo. Many patients achieve moderate to excellent repigmentation. If repigmentation efforts fail in patients with extensive depigmentation affecting more than 50% of the cutaneous surface, therapy using monobenzone may be a viable alternate.

Despite many of the prevailing myths regarding dyschromias, there are safe and efficacious therapies available for treatment of a variety of common disorders of pigmentation.

PEARL E. GRIMES, MD
Los Angeles, California

REFERENCES

Grimes PE. Psoralen photochemotherapy for vitiligo. Clin Dermatol 1997; 15:921–926

Kovacs So. Vitiligo. J Am Acad Dermatol 1998; 38:647–666

Patient-Applied Treatment for External Genital Warts: The Time has Come

GUIDELINES PUBLISHED BY the Centers for Disease Control and Prevention and the consensus of a recent American Medical Association panel have categorized two treatment approaches for external genital warts: patient-applied and provider-administered.

Provider-administered therapies include trichloroacetic acid, bichloracetic acid, podophyllin resin, cryotherapy, intralesional interferon, surgical removal, and laser surgery. Patient-applied therapies include podofilox solution or gel and imiquimod cream.

Podofilox is an antimitotic drug which may also damage endothelial cells. Patients apply podofilox twice daily for 3 days followed by 4 days off treatment. Four such treatment cycles constitute a course of treatment. Imiquimod is an interferon and Th-1 cytokine inducer. Patients apply the cream 3 times weekly (on alternate days) for up to 16 weeks.

While all of these modalities are eventually effective in rendering patients wart-free, complex factors influence treatment selection by both patient and provider. There is clearly no ideal treatment for all patients or for all warts.

Genital warts are caused by the low-risk genital human papillomaviruses (HPV) types, predominantly HPV 6. While at least 50% of the sexually active population in the U.S. are infected with one or more HPVs, only 1% have external genital warts. These HPV types have little, if any, malignant potential. As we have learned to distinguish these types from the high-risk types associated with cervical cancer, there has been a general tendency toward less aggressive therapy.

The goal of treatment of genital warts is the removal of symptoms, which can be emotional as well as physical. Physical symptoms include pain, burning, and bleeding and are relatively rare. The emotional impact of having active viral STD is significant, however.

While there is no convincing evidence that patient-applied therapies are superior to provider-administered therapies, an important consideration is patient preference. In the long term, the major effect of genital warts on many patients is not the bumps or growths, but rather the emotional consequences of this infection on them, their relationships, and their sexuality. The availability of patient-applied therapies allows the patient to have some control over this difficult problem.

The major question is whether the patient wishes the physician to treat the warts or wishes to treat the warts him/herself. In addition, there is a need for education about the natural history of HPV infection. Although HPV infection and external genital warts are common, many patients before diagnosis have heard of neither.

KARL R. BEUTNER, MD, PHD
Vallejo, California

REFERENCES

Tyring S, Edwards L, Cherry LK, Ramsdell WM, Kotner S, Greenberg MD, Vance JC, Barnum G, Dromgoole SH, Killey FP, Toter T. Safety and efficacy of 0.5% podofilox gel in the treatment of anogenital warts. Arch Dermatol 1998; 134:33–38

Beutner KR, Tyring SK, Trofatter KF, Douglas JM, Spruance S, Owens ML, Fox TL, Hougham AJ, Schmitt KA. Imiquimod, a patient-applied immune-response modifier for treatment of external genital warts. Antimicrob Agents Chemother 1998; 42:789–794

Edwards L, Ferenczy A, Eron L, et al. Self-administered topical 5% imiquimod cream for external anogenital warts. HPV Study Group. Human PapillomaVirus. Arch Dermatol 1998; 134:25–30

Lasers for Removing Unwanted Hair and Rejuvenating Skin

THE USE OF LASERS for treating a variety of skin diseases demonstrates the precision and selectivity provided by these devices that reduce the risk of complications and enhance the opportunity for a satisfactory outcome. Several of the newest uses for lasers are removing unwanted hair and rejuvenating sun-damaged or aged skin.

Removal of hair with little discomfort and excellent long-term results by light from lasers or non-laser sources can be accomplished with two different techniques. The first technique employs the topical introduction of a carbon-based material in mineral oil into the hair follicle that absorbs infrared light from a Q-switched Nd:YAG laser. The mechanism of action for this technique is a combination of thermal and mechanical injury to the germinative cells of the follicle that are in contact with the carbon particles. A second technique uses the absorption of light by melanin—found between matrix cells in the hair bulb and in the structural elements of the hair shaft medulla, cortex and cuticle—to injure the hair follicle. The mechanism of action for this group of lasers is largely thermal. In order to have an effect on hair growth, precise damage must be done to follicle germinal cells. Since the absorption spectrum for melanin is broad, many wavelengths of light from several different devices can be used to remove hair. The Food and Drug Administration (FDA) has given clearance for treating unwanted hairs to the long-pulse ruby, the alexandrite and diode lasers as well as an intense light source. Some of these devices use contact or spray cooling to reduce thermal injury to the pigmented epidermis as the treatment is being performed. The use of non-laser light from a flashlamp that produces an intense source of white light that is filtered to deliver wavelengths greater than 590 nm for effectively removing unwanted hair has recently been reported. This system allows adjustments in both the pulse duration and wavelength, depending on the clinical situation and the color the patient's skin and hair to provide additional flexibility.

All current treatment techniques for removing hair are performed in ambulatory settings either without anesthesia or with topical anesthesia alone. The treatment may produce minimal postoperative edema or transient erythema lasting 24–48 hours. Although hair follicles have tremendous regenerative capabilities that vary greatly from individual to individual and from one anatomic site to another, typically a delay in hair regrowth will average 3–6 months after a single treatment. Treating the same area sequentially as hairs begin to regrow improves the response by reducing the caliber and lightening the color of the remaining hairs and increasing the number that are permanently removed. Recently, the long-pulse ruby laser has received FDA clearance to use the term "permanent reduction" in hair following treatment, based on analysis of long-term followup data. Unlike the technique employed with electrolysis, which treats only one hair at a time, all of these new devices allow for the simultaneous treatment of many hairs with a single pulse of light, so that relatively large areas of involvement, such as the legs, chest or back, can be treated quickly. The cost of performing this treatment is generally dependent on the size of the treatment area and the time required to perform the treatment.

Treatment options for rejuvenation of sun-damaged or aged skin have been radically changed by the recent introduction of short-pulsed, high-energy carbon dioxide lasers. These devices precisely remove the solar damaged epidermis and dermis, tighten collagen, and greatly improve the appearance of most patients. However, reports of prolonged erythema, occasional scarring, and permanent hypopigmentation reduced the acceptance of

this technique and led to the introduction of the erbium:YAG laser for skin rejuvenation. The high coefficient of absorption by water for the erbium:YAG laser greatly minimizes the amount of unwanted collateral thermal injury, speeds healing time and reduces postoperative erythema. The erbium:YAG laser technique is generally most useful for younger patients or those individuals with early signs of photodamage. This is due to the fact that many more repetitions or passes are required during the single treatment session to achieve the same depth of ablation as with the carbon dioxide laser. However, reduction in side effects with this laser system make it a welcome addition to the techniques used in treating sun-damaged or aged skin. The cost of performing laser skin resurfacing is generally similar or slightly higher than the cost associated with the older dermabrasion technique but with the added benefits of greater precision, rapid healing and a more predictable outcome.

RONALD G. WHEELAND, MD
Santa Fe, New Mexico

REFERENCES

Grossman MC, Dierickx C, Farinelli W, et al. Damage to hair follicles by normal-mode ruby laser pulses. J Am Acad Dermatol 1996; 35:889–894

Goldberg DJ, Littler CM, Wheeland RG. Topical suspension-assisted Q-switched Nd:YAG laser hair removal. Dermatol Surg 1997; 23:741–745

Teikemeier G, Goldberg DJ. Skin resurfacing with the erbium:YAG laser. Dermatol Surg 1997; 23:685–687

ADVISORY PANEL TO THE SECTION ON DERMATOLOGY

SETH L. MATARASSO, MD
Advisory Panel Chair
CMA Council on Scientific Affairs Representative
San Francisco

SETH L. MATARASSO, MD
CMA Section Chair
San Francisco

RONALD L. MOY, MD
CMA Section Assistant Secretary
Los Angeles

JOHN K. GEISSE, MD
CMA Section Assistant Secretary
Vallejo

ABEL TORRES, MD
Loma Linda University Representative

OPEN
Stanford University Representative

PETER J. LYNCH, MD
University of California, Davis

RONALD BARR, MD
University of California, Irvine

ROBERT L. MODLIN, MD
University of California, Los Angeles

ROBERT W. GOLTZ, MD
University of California, San Diego

RICHARD B. ODOM, MD
University of California, San Francisco

THOMAS REA, MD
University of Southern California

A. PAUL KELLY, MD
Charles R. Drew University of Medicine and Science, Los Angeles

COMRON MALEKI, MD
President
Thousand Oaks

JOSEPH COLLEGE, MD
President-Elect
Escondido

NORMAN C. STIRLING, MD
Past President
Marina del Rey

VICTOR D. NEWCOMER, MD
CMA Delegate
Santa Monica

ROBERT T. CARSON, MD
CMA Alternate Delegate
Oxnard

PATRICIA A. COGHLAN, MD
Executive Secretary
Los Angeles

KATHRYN DUKE
CMA Staff
San Francisco

Alerts, Notices, and Case Reports

A Novel Approach to Understanding a Mysterious Murmur in a Young Adult After Surgical Repair of Tetralogy of Fallot

COL JAMES B. KINNEY, JR, MC, USA
VINCENT B. HO, MD
CPT KATHERINE M. MIZELLE, MC, USAR
Tacoma, Washington
DAVID J. SAHN, MD
Portland, Oregon

THE DEVELOPMENT OF bronchopulmonary collateral arteries is a natural response in patients born with cyanotic congenital heart disease.[1] Even after successful corrective surgery, these collateral arteries may remain a concern: they can be responsible for unusual murmurs, clinical symptoms, or hemodynamic changes resulting from the increase in pulmonary blood flow. Despite earlier successful surgical management for tetralogy of Fallot, a young adult had a persistent loud continuous murmur, the origin of which was unknown. Doppler ultrasound suggested the presence of bronchopulmonary collateral vessels. Breath-hold gadolinium-enhanced magnetic resonance angiography (MRA) clearly delineated a large bronchopulmonary collateral artery. The MRA technique and case history are described.

Report of a Case

Our patient, a 29-year-old woman, was born with a heart murmur that was originally believed to be a ventricular septal defect. Beginning at 6 months of age, she began to develop questionable cyanosis. Cardiac catheterization at 12 months of age established the diagnosis of tetralogy of Fallot (pulmonary stenosis, ventricular septal defect, dextraposition of the aorta, and hypertrophy of the right ventricle). No collateral vessels were found, but an occlusion aortogram was not performed. Although the patient experienced gradually worsening cyanosis, because of surgical risk and general management strategies at the time, it was not until she was 5 years old that her parents consented to open heart surgery, which was just beginning to be performed on children in her community.

At surgery, the ventricular septal defect was closed with a patch, while a pericardial patch was used to enlarge the pulmonary outflow tract. No comment was made by the surgical staff about the atrial septum. A repeat cardiac catheterization 2 years after surgery demonstrated an oxygen step-up at the atrial level, but the repair was otherwise thought to be adequate. Again, no large bronchopulmonary vessels were identified.

Twenty-three years later, having moved to a different city, the patient experienced insidious onset of dyspnea with exertion and was referred to an adult cardiology service. On physical examination, she had a grade 2/6 systolic ejection murmur over the base of the heart and a grade 3/4 decrescendo diastolic murmur at the mid-left sternal border. One observer detected a second continuous murmur in the right chest.

Left and right heart catheterization was performed with angiography. The repair was demonstrated to be intact. There was a 40-mm systolic right ventricular to pulmonary artery gradient. A main pulmonary artery arteriogram documented severe pulmonary insufficiency, and a large atrial septal defect shunt was seen on levophase. By oximetry, the pulmonary to systemic flow for the shunt across the atrial septal defect was calculated to be 3:1. An ascending aortogram performed just above the aortic valve failed to identify any specific collateral vessels; however, there was a suggestion of contrast dye in the right lung on retrospective review of the permanent filmed cine angiogram.

The patient underwent repeat surgery with a patch closure of the atrial septal defect, and a homograft pulmonary valve was placed. The patient recovered uneventfully and was asymptomatic. One year later her follow-up exam revealed a grade 2/6 to 3/6 continuous murmur over the right chest and back. A Doppler ultrasound study suggested some arterial flow shunting into the right lung, but the air-filled lung in the region in question precluded high quality imaging. Because she was asymptomatic, the patient was resistant to invasive repeat cardiac catheterization. She was referred to the pediatric cardiology service to solicit additional recommendations.

To evaluate the origin of the Doppler signal in the right lung, an MRA was performed using a 1.5-tesla magnetic resonance scanner (General Electric Medical Systems, Signa version 5.4, Milwaukee, WI). Standard electrocardiogram-gated spin-echo T1-weighted images were obtained in coronal, axial, and sagittal planes. On axial T1-weighted images, there was interruption of the right lateral wall of the descending aorta, suggesting a dilated bronchial collateral artery. A coronal breath-hold

(Kinney JB, Ho VB, Mizelle KM, Sahn DJ: A novel approach to understanding a mysterious murmur in a young adult after surgical repair of tetralogy of Fallot. West J Med 1998 169:230–231)

From the Departments of Pediatrics (COL Kinney and CPT Mizelle) and Radiology (Dr Ho), Madigan Army Medical, Center, Tacoma, Washington, the Department of Radiology (Dr Ho), Uniformed Services University of the Health Sciences, Bethesda, Maryland, and the Clinical Care Center for Congenital Heart Disease (Dr Sahn), Oregon Health Science University, Portland, Oregon.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or reflecting the views of the Department of the Army, Department of Defense, or Uniformed Services University of the Health Sciences.

Reprint requests to COL James B. Kinney, Jr, MD, Madigan Army Medical Center, Tacoma, WA 98431.

ABBREVIATIONS USED IN TEXT
MRA = magnetic resonance angiography

three-dimensional spoiled gradient echo MRA (repetition time 11 msec, echo time 1.9 msec, flip angle 45 degrees, one excitation) of the pulmonary vasculature was performed in conjunction with a 40-ml hand-injected intravenous bolus of gadolinium-chelate contrast medium (Prohance, Bracco Diagnostics, Princeton, NJ).[2] The MRA revealed a large bronchial collateral artery originating from the descending aorta and draining into the hilus of the right lung (Figure 1).

After diagnosis, the patient moved away from the area. She was counseled regarding catheterization procedures to occlude the collateral artery and, at last follow-up, intended to undergo an occlusion procedure.

Figure 1.—Gadolinium-enhanced three-dimensional MRA. Coronal, single-voxel reformation from a 46-second breath-hold acquisition clearly demonstrates the dilated bronchial collateral emanating from the right side of the descending thoracic aorta (arrow).

Discussion

Large bronchopulmonary collateral arteries are a challenge in managing the patient with surgically corrected congenital cyanotic heart disease. The flow through the collateral arteries will continue to function as if there had been no corrective intracardiac procedure.[3,4] If a bronchopulmonary collateral artery enlarges substantially, the additional pulmonary flow "competes" with the normal pulmonary perfusion, resulting in an increased mean pulmonary artery pressure, and eventually, increased pulmonary vascular resistance. In addition, an expanding serpiginous collateral vessel may erode tissue of the affected lung.[5] Collateral flow has become an increased concern since the introduction of the Fontan procedure, as any competing circulation jeopardizes the long-term prognosis of the patient undergoing that procedure.[6]

When identified, bronchopulmonary collateral arteries can often be occluded with Gianturco coils, sponges, or balloons in the cardiac catheterization laboratory.[7] However, no standard noninvasive screening method for identifying these arteries has been developed. Gadolinium-enhanced MRA has been successfully used to study branch vessels arising from the thoracic aorta in adults.[2] Encouraged by the experience of Vick et al.[8] with cine gradient-echo magnetic resonance evaluation of collateral arteries, we performed breath-hold gadolinium-enhanced MRA to better delineate the clinically suspected bronchopulmonary collateral vessel in our patient.

Gadolinium-enhanced MRA images parallel traditional angiograms and are readily interpreted by surgeons and interventional cardiologists. By all parameters, the gadolinium-enhanced images clearly eclipsed in detail the evanescent noncontrast studies. Although Vick et al.[8] have shown cine gradient-echo magnetic resonance to be adequately sensitive for identifying the presence of significant bronchopulmonary collateral arteries, we propose that gadolinium-enhanced MRA should be considered as an alternative, and possibly superior, method for managing cooperative adolescents and adults with postoperative cyanotic heart disease. The described gadolinium-enhanced MRA is a three-dimensional technique that promises higher resolution than the two-dimensional cine gradient-echo and can be performed in less time for a given anatomic region.

It is also apparent from this case that regional difference in blood flow distribution (probably the major determinant of collateral vessel growth) may exist even after apparently successful repair in tetralogy of Fallot, and continued surveillance is required.

REFERENCES

1. Liberthson RR, Miller SW, Drew F, Palacios I, Singh J: Congenital extracardiac shunts with tetralogy of Fallot. Cardiovasc Intervent Radiol 1981; 4:131–135

2. Prince MR, Narasimham DL, Jacoby WT, Williams DM, Cho KJ, Marx MV, Deeb GM: Three-dimensional gadolinium-enhanced MR angiography of the thoracic aorta. Am J Roentgenol 1996; 166:1387–1397

3. Rabinovitch M, Herrera-deLeon V, Castaneda AR, Reid L: Growth and development of the pulmonary vascular bed in patients with tetralogy of Fallot with or without pulmonary atresia. Circulation 1981; 64:1234–1249

4. McGoon DC, Baird DK, Davis GD: Surgical management of large bronchial collateral arteries with pulmonary stenosis or atresia. Circulation 1975; 52:109–118

5. McGoon MD, Fulton RE, Davis GD, Ritter DG, Neill CA, White RI Jr: Systemic collateral and pulmonary artery stenosis in patients with congenital pulmonary valve atresia and ventricular septal defect. Circulation 1977; 56:473–479

6. Warnes CA: Tricuspid atresia and univentricular heart after the Fontan procedure. Cardiology Clin 1993; 11:665–673

7. Perry SB, Radtke W, Fellows KE, Keane JF, Lock JE: Coil embolization to occlude aorticopulmonary collateral vessels and shunts in patients with congenital heart disease. J Am Coll Cardiol 1989; 13:100–108

8. Vick GW, Wendt RE, Rokey R: Comparison of gradient echo with spin echo MRI and echocardiography in the evaluation of major aortopulmonary collateral arteries. Am Heart J 1994; 127:1341–1347

Case Presentation and Review: Constrictive Pericarditis

LARS OSTERBERG, MD
RANDALL VAGELOS, MD
J. EDWIN ATWOOD, MD
Palo Alto, California

CONSTRICTIVE PERICARDITIS (CP) is present when a thickened and adherent pericardium restricts diastolic filling of the heart. Tuberculosis was once a common cause of CP, whereas nowadays most cases are idiopathic.[1] Previously known as Pick's Disease, CP often is referred to as pseudocirrhosis because it clinically can mimic chronic liver disease.[2,3] Patients with CP frequently have hepatomegaly, marked pitting lower extremity edema, and ascites with liver function tests indicative of passive congestion. The key differentiation from liver disease is the elevated jugular venous pressure. The possible presence of Kussmaul's sign and the pericardial knock also help distinguish CP. Echo-Doppler cardiography, a diagnostic tool, excludes other diseases and has the superior ability to evaluate diastolic flow and function. Patients suspected of having CP should undergo right heart catheterization in order to document equalization and elevation of filling pressures. With the improvement of imaging techniques, the diagnosis can be supported by CT or MRI scanning with a high degree of sensitivity. The dramatic improvement resulting from pericardial stripping in patients who have not progressed to advanced stages of heart failure points to the importance of recognizing this uncommon yet potentially curable form of heart failure.

Clinical Presentation

A 48-year-old man was referred to a clinic with a three-year history of anasarca and lower extremity edema which were partially responsive to the medications lasix and spironolactone. The patient was told his symptoms were partially a result of his history of alcohol abuse. Although he had suffered chronic obstructive lung disease with an FEV1 of 66% of normal, he had not had tuberculosis and was PPD negative. His medications were lasix 60 mg. BID and spironolactone 50 mg. QD. On physical examination his blood pressure was 115/63; pulse, 87; respirations, 18; and he was not febrile. There was a pulsus paradoxus of 15 mmHg. He had no spider angioma or icterus. His neck veins were distended, and his lungs were clear to auscultation. On cardiac exam he had a regular rhythm, with a soft I/VI systolic murmur at the apex. He had an enlarged liver percussed at 20 cm, a fluid wave with bulging flanks, and marked pitting edema to his knees bilaterally (Table 1).

The patient was referred to cardiology for a right and left heart catheterization and biopsy. Right heart catheterization was consistent with diastolic equalization of pressures (Figure 1), and hemodynamic representation of Kussmaul's sign was seen (Figure 2). Simultaneous right and left heart catheterization showed elevation and equalization of right sided and left sided diastolic filling pressures, with characteristic dip and plateau (Figures 3 and 4). The patient's arterial tracing demonstrated a pulsus paradoxus of 15 mmHg (Figure 5). No evidence of left to right shunt by sampling venous blood in the right heart chambers was noted.

The patient underwent non contrast computed tomography of the chest which confirmed a thickened pericardium of 5 mm (normal <4 mm), and pericardial stripping resulted in marked resolution of his symptoms.

This case demonstrates the clinical similarities of CP and chronic liver disease, yet also points out features that distinguish the two. Most importantly, the jugular venous pressure (JVP) of the CP patient is elevated, but is usually normal in patients with cirrhosis. In fact, astute observation reveals a sudden collapse of the JVP (rapid y-descent) in patients with CP (Figure 2). Furthermore, patients with long-standing cirrhosis usually have small nodular livers, and patients with CP frequently have enlarged, smooth livers. The liver function tests in patients with CP may have a pattern of passive congestion with more prominent elevations of alkaline phosphatase and GGT than transaminases, and cirrhotic patients often have more diminished synthetic function with decreased albumen and elevated protime and, possibly, elevated transaminases (Table 2). Because of CP chronicity, the finding of decreased liver synthetic function with a depressed serum albumen makes the liver function tests poor for distinguishing CP from chronic liver disease.

Although an elevated JVP can help distinguish patients with CP from patients with cirrhosis, the conditions of cardiac tamponade, right ventricular infarction, and restrictive cardiomyopathy all can produce an elevated JVP and appear clinically similar to CP. A rapid y-descent of the JVP supports the diagnosis of CP. In addition, the pericardial knock is only found in CP, but it is heard in just one-third to one-half of cases.[4] The pericardial knock, heard best with the diaphragm of the stethoscope, occurs 0.6-0.12 seconds after S2—not to be confused with an S3, which is of lower frequency—and corresponds to the rapid cessation of ventricular filling.[4] Given the variable degree in which various physical findings are recorded in the literature (Table 3),[2,3,5-7] one is often left with the differential diagnosis of CP, tamponade, and restrictive cardiomyopathy when embarking on the diagnostic workup.

Introduction

Constrictive pericarditis, defined as impedance to diastolic filling caused by a fibrotic pericardium, may be a

(Osterberg L, Vagelos R, Atwood JE. Case presentation and review:constrictive pericarditis. West J Med 1998; 169:232-239)

From the Stanford University School of Medicine, Palo Alto, California.

Reprint requests to Lars Osterberg, MD, General Medicine Attending, VA Palo Alto Health Care System and Clinical Instructor, Department of Medicine, Stanford University School of Medicine, Mail Code 111A, 3801 Miranda Ave, Palo Alto, CA 94304.

ABBREVIATIONS USED IN TEXT

JVP = jugular venous pressure
MRI = magnetic resonance imaging
CP = constrictive pericarditis
CT = computed tomography

long-term consequence of chronic pericarditis following an acute episode. The visceral and parietal pericardium usually become adherent with obliteration of the pericardial space, but in some cases the constricting process is formed by the visceral pericardium (epicardium) alone.[5,8] As the disease progresses, calcium deposition may occur with further thickening and stiffening of the pericardium. Constriction is usually symmetric although localized areas or bands of constriction have been reported.[9,10] The term effusive constrictive pericarditis, popularized by Hancock, is used to refer to cases in which constrictive pericarditis coexists with a tense pericardial effusion.[11]

History

Descriptions of diseases of the pericardium have a long history and date back as far as Egyptian and Greek civilizations. One of the early descriptions of CP was by Richard Lower in 1669 who described a patient with dyspnea and an intermittent pulse. Kussmaul, in 1873, coined the term pulsus paradoxus for the phenomenon of an intermittent loss of pulse during inspiration despite still hearing the heartbeat. In 1896, the term Pick's disease was given to patients who had ascites and hepatomegaly (pseudocirrhosis) in the setting of CP. See Table 4 for a summary of major historical events.[2,12]

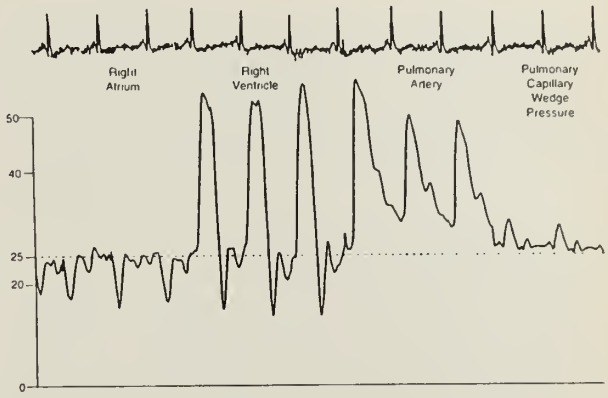


Figure 1.—Right atrial, right ventricular, pulmonary artery, and pulmonary capillary wedge hemodynamic tracings from a patient with CP. Note the diastolic equalization of pressures (less than 5 mm difference) and the pronounced x and y descent of the right atrial tracing.

Pathophysiology

The normal pericardium—a strong, thin sac surrounding the heart with fibrous tissue extending to the adventitia of the great vessels—is composed of two layers: a tough, fibrous layer (the parietal pericardium) and a smooth, serous layer (the visceral pericardium) which is intimately apposed to the heart's surface and epicardial fat. The normal visceral and parietal pericardium allow the heart to move around freely with uninhibited expansion of the cardiac chambers during diastole. This expansion provides for an unimpeded atrial contribution to diastolic filling, which has been reported to increase cardiac output by as much as 30%. With CP, however, the thickened, fibrotic pericardium has a relatively fixed diastolic volume which does not allow for

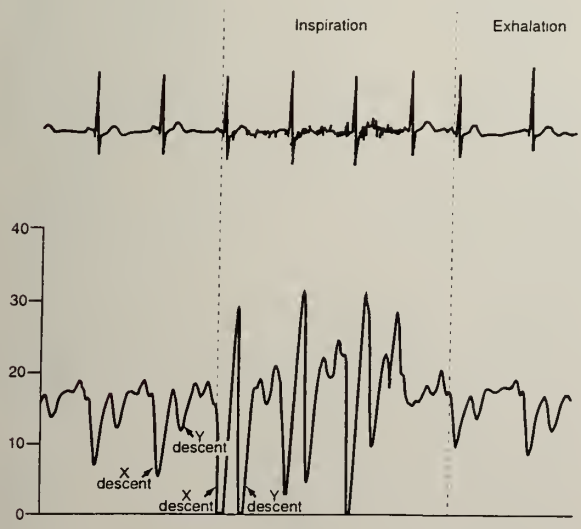


Figure 2.—Kussmaul's sign on hemodynamic tracing. Note the exaggerated x and y descent particularly during inspiration.

Figure 3.—Simultaneous right ventricular and left ventricular tracings. Note the close approximation of diastolic pressures.

Figure 4.—Simultaneous right ventricular and left ventricular tracings. Note the near equalization of diastolic pressures, the rapid filling wave (√) which are most pronounced following a premature ventricular contraction.

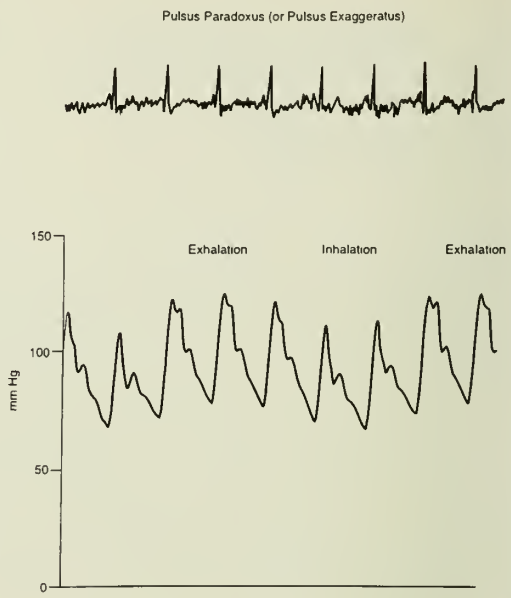


Figure 5.—Aortic pressure tracing demonstrating a greater than 15 mm respiratory change in systolic pressure consistent with pulsus paradoxus (or pulsus exaggeratus).

complete unimpeded filling. The cardiac chambers fill freely in early diastole because the volume in the cardiac chambers is low. But, as the cardiac chambers rapidly fill, and the volumes reach the threshold set by the thickened noncompliant pericardium, diastolic filling is abruptly halted. This sudden cessation may contribute to the exaggerated effect of ventricular interdependence (or coupling) with relatively more blood in the right atrium and right ventricle than in the left sided chambers during inspiration (Figure 6).

Pressure tracings of ventricular filling in patients with CP show that nearly all ventricular filling occurs in the first third of diastole with little filling after this because of the restraining effect of the thickened pericardium. This drop in activity accounts for the rapid y-descent and plateau seen in the JVP on physical exam, and in the right atrial, right ventricular and left ventricular pressure tracings during cardiac catheterization. The rapid y-descent represents the pressure in initial unimpeded chamber filling of early diastole, whereas the plateau represents the pressure at the fixed diastolic volume of mid- and late diastole as determined by the thickened pericardium. This dip and plateau on hemodynamic tracings is known as the "square root sign" (Figure 4).

The fixed diastolic volume determined by the thickened pericardium causes both right and left heart diastolic pressures to be elevated to the same degree (within 5 mmHg) in all four cardiac chambers. Thus, right atrial pressure, right ventricular diastolic pressure, and pulmonary capillary wedge pressure which indirectly represents left atrial and left ventricular diastolic pressures may all be nearly the same during right heart catheterization, a condition often referred to as diastolic equalization of pressures (Table 5). Furthermore, simultaneous right and left ventricular pressure tracings reveal almost a superimposition of the diastolic pressure tracings (Figures 3 and 4).

The mechanism of Kussmaul's sign is still debated, although one explanation is that the rigid pericardium in CP fails to transmit intrathoracic pressure variations to the heart's chambers.[13] Because the rigid pericardium in CP

TABLE 1.—*Laboratory Results*

Urinalysis: normal with no protein		
Alkaline Phosphatase: 153		SGOT: 26 SGPT: 18
Total Bilirubin: 1.9	Albumen: 3.9	Protime: 11.8 (INR = 1.0)
BUN: 13	Creatinine: 1.1	WBC: 7.3 Hemoglobin: 15.5
Hematocrit: 45.9%	Platelets: 226,000	MCV: 86

CXR: Normal cardiac sillhouette without pulmonary venous congestion
EKG: Normal sinus rhythm with borderline low voltage.
Echocardiogram: Biatrial enlargement, normal valvular function, and normal right ventricular and left ventricular systolic function with evidence of pericardial thickening. The Doppler mitral inflow pattern was suggestive but not diagnostic of constrictive physiology.

TABLE 2.—*Liver Function Tests: Passive Congestion vs. Cirrhosis*

	RV Failure	*Cirrhosis*
T. Bili.	↑	↑↑
Alk. Phos.	↑↑	↑
AST/ALT	usually nl	↑↑
Albumen	usually nl	↓
PT/INR	↑ or nl	↑↑

TABLE 3.— *Prevalence of Various Physical Examination Findings*

- Pulsus paradoxus usually absent (14-84%)
- Jugular veins distended (99-100%) - prominent y-descent
- Kussmaul's sign
- Pericardial knock/S3 (5-55%)
- Hepatomegaly (70-100%)
- Splenomegaly
- Ascites
- Peripheral edema (64-80%)

TABLE 4.—*Major Historical Events in Constrictive Pericarditis*

- 1669 Richard Lower describes a patient with dyspnea and intermittent pulse.
- 1842 Corrigan describes the pericardial knock (bruit de frappement).
- 1873 Kussmaul names the "paradadoxical arterial pulse," pulsus paradoxus.
- 1896 The eponym Pick's disease is given to patients with constrictive pericarditis who have ascites and hepatomegaly (pseudocirrhosis).
- 1929 The first successful pericardiectomy in the United States is performed by Ed Churchill.
- 1935 Paul Dudley White describes 7 of 15 patients with constrictive pericarditis who were successfully operated on at the Massachussetes General Hospital.
- 1946 Bloomfield demonstrates elevated right ventricular pressure with early dip and plateau in patients with constrictive pericrditis.
- 1982 Isner demonstrates the value of computed tomography in the diagnosis of constrictive pericarditis.

does not allow for right atrial and right ventricular expansion during inspiration, the increased venous return that occurs in inspiration results in a rise in central venous pressure. Another proposed explanation is that there is a normal inspiratory increase of intra-abdominal pressure transmitted to a tense overly filled venous system caused by CP.[14] Figure 6 is a schematic drawing demonstrating the mechanism of pulsus paradoxus (the drop in arterial pulse pressure during respiration [Figure 5]), a sign often seen in CP. Occasionally, cases of CP are seen without a pulsus paradoxus since the thickened pericardium can completely isolate the heart from the effects of respiration.[4]

Etiology

Tuberculosis is still the leading cause of CP in developing countries, but accounts for only a minority of cases in western cultures.[15] Most cases of CP in developed countries have no known antecedents although the possibility has been suggested that these cases are stem from an apparent previous episode of viral pericarditis.[3] The frequency of radiation therapy as a cause can be influenced by the patients recruited to the series. For example, post-radiotherapy was cited as a cause of CP in 31% of patients in a Stanford series and was the etiology in only 5% in a Mayo series.[8,16] This discrepancy likely reflects the fact that Stanford is a large referral center for patients with Hodgkin's disease who often receive mediastinal radiation. The list of etiologies of CP are listed in Table 6.[2-4]

Diagnostic Evaluation

Routine studies such as ECG and chest radiographs usually are helpful only in supporting a search for pericar-

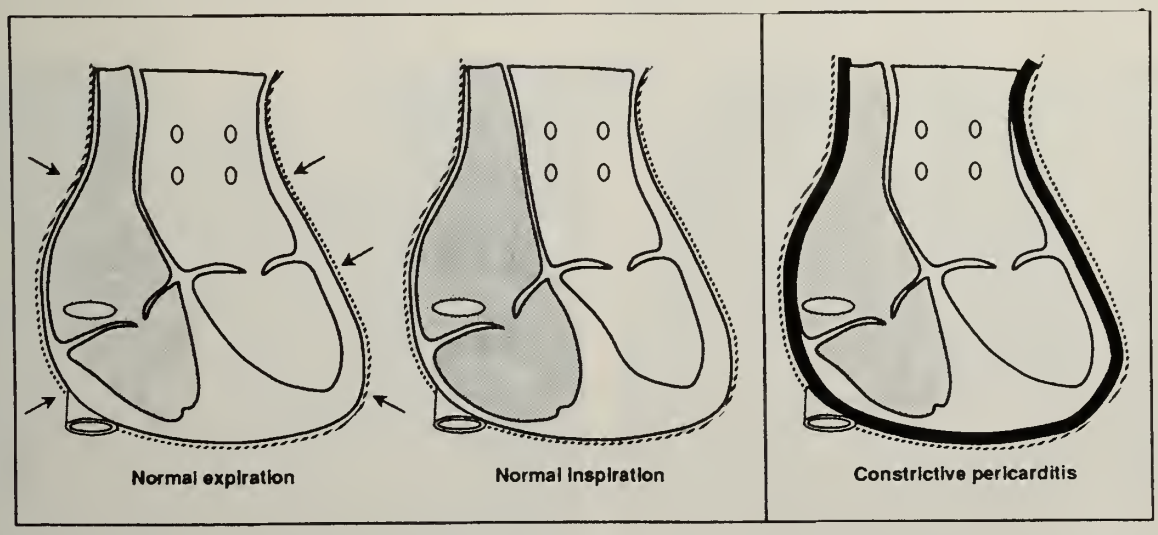


Figure 6.—Schematic drawing of the proposed physiology of pulsus paradoxus. Note the effects of inspiration on the right atrium and right ventricle in the normal heart causing bowing of the interventricular septum and a resultant decrease in left ventricular preload and therefore a decreased pulse. In constrictive pericarditis, however, a thickened and rigid pericardium can prevent transmission of intathoracic pressure variations to the right atrium and right ventricle resulting in little effect of respiration on the intracardiac pressures and hence little pulse pressure variation with respiration.

TABLE 5.—*Causes of Diastolic Equalization of Pressure**

Constrictive pericarditis
Pericardial tamponade
Restrictive cardiomyopathy
End stage dilated cardiomyopathy (All pressures high)
Dehydration (All pressures low)
Atrial septal defect
Hyperinflated lungs (COPD, pneumothorax)

*Less than 5 mm difference between right atrial and left atrial (pulmonary capillary wedge pressure), right ventricular and left ventricular diastolic pressure.

TABLE 6.—*Major Categories of Etiologies of Constrictive Pericarditis*

1. Idiopathic
2. Infectious:
   - Tuberculosis
   - Viral esp. Coxackie B
   - Bacterial
   - Fungal
   - Parasitic
3. Post radiotherapy
4. Post cardiac surgery
5. Post traumatic
6. Neoplastic
7. Connective tissue diseases
   esp. rheumatoid arthritis and SLE
8. Toxic/Metabolic
   uremia, chylous pericardium, methysergide
9. Post myocardial infarction
10. Familial

dial constriction and not for making a diagnosis. The findings on ECG, though rarely normal, are nonspecific and highly variable. Atrial arrhythmias frequently are seen with atrial fibrillation being a common late occurrence. Low voltage is seen less than 50% of the time, and left atrial enlargement is variable, ranging from 19-37% of cases.[17] The chest radiograph can reveal an enlarged cardiac silhouette, and pulmonary venous congestion and pleural effusions often are seen late in the disease. A calcified pericardium seen on a chest radiography is highly suggestive of CP when it is present in a patient with constrictive/restrictive physiology (Figure 7).[18] With the previous exceptions, the signs on ECG and chest radiographs are insensitive indicators of pericardial constriction. Cardiac catheterization often is required to document restrictive/constrictive physiology, and special imaging studies may be needed to prove the presence of a thickened pericardium.

Echo Doppler

Numerous non-specific echocardiographic findings in CP also may be found individually in other diseases. Although echocardiography is insensitive in determining pericardial thickening, certain echocardiographic signs present in the appropriate clinical setting may argue strongly for the diagnosis of CP.[10] Often these echo findings are consistent with the physiology of CP: early rapid diastolic filling of the ventricles with little distension late in diastole because of a thick fibrous indistensible pericardium. Right and left ventricular systolic function is usually normal, however, because right and left ventricular cavity dimensions generally are preserved and systolic wall motion is normal. High atrial pressures may lead to right atrial and left atrial enlargement, inferior vena caval plethora, and prominent early diastolic ventricular filling causing exaggerated septal and posterior wall motion filling pattern.[19,20] The exag-

Figure 7.—Posterior-anterior and lateral chest radiograph demonstrating a thickened calcified pericardium in another patient with CP (Courtesy of Paul Stark).

TABLE 7.—*Echocardiographic and Doppler Signs of CP*

M-mode and Two D echo:

- Pericardial thickening
- Normal RV and LV chamber size
- Lefl atrial and right atrial enlargement
- Abnormal septal motion and posterior wall motion Paradoxical septal motion Diastolic septal bounce
- Premature opening of the pulmonic valve
- Dilated inferior vena cave without respiratory variation

Doppler Findings:

- Superior Vena Cava: Diastolic Flow Velocity > Systolic Flow Velocity
- Hepatic Vein: Exaggerated diastolic flow reversal afler onset of exhalation
- Pulmonary Venous Flow: Increase in diastolic flow velocity on exhalation Systolic/Diastolic flow velocity ratio < .65 Peak Diastolic flow velocity falls 40% on inspiration
- Mitral Inflow Pattern: During onset of exhalation 2 25% increase in early diastolic flow velocity

gerated response to respiration may lead also to abnormal atrial and ventricular septal motion seen on routine transthoracic echo but often is best noted on transesophageal images.

Adding a new dimension to the evaluation of diastolic function, Doppler echocardiography has become extremely useful not only in diagnosing CP but differentiating it from restrictive cardiomyopathy. Again, many of the findings may be nonspecific and are found in patients either with exaggerated breathing patterns of pulmonary disease or with right ventricular infarction. Some findings are listed in Table 7, and more technical explanations of the mechanisms for these findings can found in References.[19, 21-24, 29]

Hemodynamics

The hallmark of the hemodynamic evaluation of CP is diastolic equalization of pressure (less than a 5 mm difference between right and left atrial pressures and right and left ventricular diastolic pressures) at an elevated level. The encasement of the heart by a thick non-compliant pericardium as noted earlier leads both to this equalization of pressure and to a lack of transmitted intrathoracic pressure changes upon the heart. The vascular structures in the thoracic cavity (the superior and inferior vena cava) continue to be affected by the respiratory changes in the thoracic cavity. Consequently, inspiration allows more filling of the right atrium and right ventricle causing increased right atrial and right ventricular septal impingement on the left atrial and left ventricular cavities which have received less venous filling because of pulmonary venous pooling during inspiration (Figure 6).[25] During exhalation the reverse occurs. Exaggerated inspiratory right atrial pressures and filling patterns referred to as Kussmaul's sign may be noticeable on the pressure tracings (Figure 2) . Less frequently, one may note also an exaggerated difference between aortic systolic pressure during inspiration and exhalation, historically called "pulsus paradoxus" but more appropriately called "pulsus exaggeratus" because it is an exaggeration of a normal physiologic phenomenon of a decrease in pulse pressure with respiration (Table 8). Figure 1 shows the hemodynamic tracings of this patient with CP, demonstrating diastolic equalization of pressure.

TABLE 8.—*Causes of Pulaus Paradoxus (Pulsus Exaggeratus)*

- Pericardial Tamponade
- Exaggerated Respiratory Motion
- Asthma
- Decompensated Obstructive Lung Disease
- Effusive Constrictive Pericarditis
- Constrictive Pericarditis
- Restrictive Cardiomyopathy

Other tracings from this same patient demonstrate the similarity of the diastolic pressures of the right and left ventricle. Often this pressure similarity may be made clear after a premature ventricular contraction or during inspiration (Figures 3 and 4). If the heart rate is slow enough, a "√" configuration may be noticeable because of the exaggerated rapid filling wave and pressure plateau secondary to lack of further ventricular filling. In an attempt to differentiate CP from restrictive cardiomyopathy, physicians have used other criteria, such as the ratio of right ventricular diastolic pressure to systolic pressure of less than 1 to 3 and right sided systolic pressures of less than 55 mmHg found more commonly in CP (Table 9).[26,27] None of these hemodynamic findings alone are diagnostic of CP but only consistent with it. All of the numerous other causes of diastolic equalization of pressure, as noted in Table 5, should be excluded before diagnosing CP. Restrictive cardiomyopathy with amyloidosis is the most likely to simulate CP.[27,28] In cases where all of the diastolic pressures remain low and there is a suspicion of CP, a one-liter intravenous fluid bolus may be given to look for continued diastolic

TABLE 9.—*Hemodynamic Catheterization Findings of Constrictive Pericarditis*

1. A left ventricular diastolic and right ventricular diastolic pressure difference of less than 5 mmHg at rest. This becomes more obvious post PVC and one beat after onset of inspiration.
2. Diastolic dip and plateau (square root sign) of ventricular tracing. Prominent rapid filling wave.
3. Lack of respiratory variation or an increase in right atrial pressure on inspiration (Kussmaul's sign).
4. Right ventricular end-diastolic pressure to right ventricular systolic pressure ratio greater then 1/3.
5. Right ventricular systolic or pulmonary artery pressure greater than 55 mmHg.

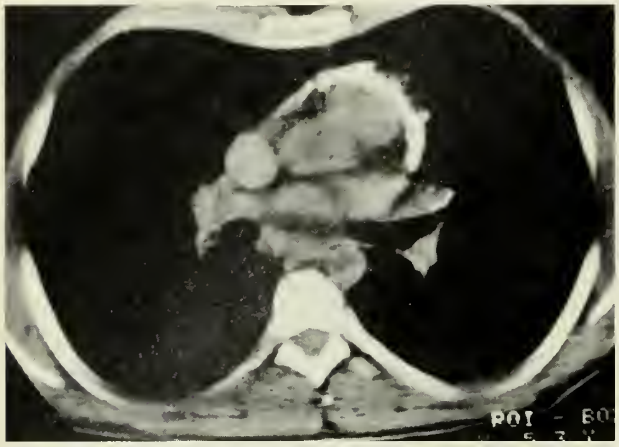


Figure 8.—Computed tomography of the chest in another patient with CP demonstrating a thickened pericardium (>4 mm.) (Courtesy of Paul Stark).

equalization of pressure (so-called occult constrictive pericarditis).[30] In normal dehydrated patients, the right and left ventricular diastolic pressures will begin to separate by more than 5 mmHg after fluid challenge. In cases of CP, the right and left ventricular diastolic pressures may rise but will not separate.

Imaging Modalities

The enhanced resolution of radiologic imaging has improved the sensitivity in detecting evidence for pericardial constriction. Computed tomography (CT) and magnetic resonance imaging (MRI) showing a thickened pericardium (Æ4 mm in most studies) in a patient with a hemodynamic profile consistent with constrictive/restrictive physiology is considered diagnostic of CP until proven otherwise (Figure 8).[12,31-35] The sensitivity of CT and MRI, however, range from 75-100%, and many cases of CP have been reported in patients whose pericardium is of normal thickness.[2] Therefore, pericardiectomy still may be the only way to confirm the diagnosis in patients whose hemodynamic profile suggests constriction but imaging is unable to document pericardial thickening, and a diagnosis cannot be confirmed by endomyocardial biopsy.[37]

Treatment

Although relatively asymptomatic patients can be managed initially with diuretics, particularly if the diagnosis is not as clear cut as expected, pericardiectomy with complete decortication of the ventricular pericardium is the treatment of choice for CP. The left anterolateral thoracotomy approach is preferred by some surgeons, although most prefer to do a median sternotomy with or without cardiopulmonary bypass.[35] This approach permits greater mobilization of the heart and allows for complete removal of the ventricular pericardium, including the entire diaphragmatic pericardium.[5,16,38] In some cases of CP, constrictive physiology is still found postoperatively despite complete removal of the parietal pericardium. Reoperation with removal of a fibrous epicardium has proven successful in some of these cases with a "constrictive epicardium," but is hazardous to the patient because of the proximity of the epicardial vessels.[5,8] Failure to improve postoperatively may result from inadequate decortication of all fibrous parietal and visceral pericardium. Other factors, such as myocardial atrophy and progressive ventricular dilation, may result in postoperative heart failure.[16] In hemodynamics, days or weeks of cardiopulmonary support often are required before gradual improvement is accomplished.

The operative mortality is highly dependent on the preoperative NYHA functional class status. In a series of 313 patients at the Mayo Clinic (from 1936-1990), the operative mortality was 1% for patients in class I or II, 10% for patients in class III, and 46% for patients in class IV status, with an overall mortality of 14%.[5] Similar mortality rates for patients in the different NYHA classes have been reported in other series with overall mortality rates ranging from 5-15%.[6,16] Other preoperative risk factors include degree of right ventricular end diastolic pressure, diuretic use, renal insufficiency, and the presence of radiation pericarditis. Risk factors found intraoperatively that worsen prognosis include the presence of unresectable calcifications or incomplete pericardial decortication.[5,6,8,16]

In general, patients with CP have a good outcome when their disease process is discovered early in its course.[6,38] Physicians must be able to recognize the subtle differences in clinical presentation of patients with CP, restrictive cardiomyopathy, pericardial tamponade, right ventricular failure, and chronic liver disease. Careful physical examination with close attention to the neck veins, a cardiac exam, and determination of liver size and texture with the appropriately directed diagnostic studies are important for recognizing this rare disease. Since surgery often results in a dramatic improvement in symptoms with the best prognosis in patients with early disease, cardiology referral for cases of suspected CP is most important. Given the highly curable nature of this disease, in cases where constrictive/restrictive physiology is present and imaging studies do not demonstrate a thickened pericardium, cardiothoracic surgery referral for diagnostic and therapeutic pericardiectomy still may be warranted.

Acknowledgment

We would like to give a special thank you to Dr. Rachel Marcus and Dr. Victor Froelicher for reviewing this manuscript and providing their expert advice.

REFERENCES

1. Shabetai R. Constrictive pericarditis. *In* Shabetai R (Ed): The pericardium. New York: Grune & Stratton; 1981, ch 4

2. Fowler NO. Constrictive pericarditis: Its history and current status. Clin Cardiol 1995; 18:341-350

3. Cameron J, Oesterle SN, Baldwin JC, Hancock EW. The etiologic spectrum of constrictive pericarditis. Am Heart J 1978; 96:110-122

4. Brockington GM, Zebede J, Pandian, NG. Constrictive pericarditis. Cardiology Clinics 1990; 8(4):645-660

5. Tuna IC, Danielson GK. Surgical management of pericardial diseases. Diseases of the Pericardium 1990; 8(4):683-696

6. Bashi VV, John S, Ravikumar E, Jairaj PS, Shyamsunder K. Early and late results of percardiectomy in 118 cases of constrictive percarditis. Thorax 1988; 43:637-641

7. Wise DE, Conti CR. Constrictive pericarditis in pericardial diseases; Cardiovascular Clinics 1976; 7(3):197-210

8. Seifert FC, Miller C, Oesterle SN, Oyer PE, Stinson EB, Shumway NE. Surgical treatment of constrictive pericarditis: analysis of outcome and diagnostic error. Circulation 1985; 72(suppl II):264-273

9. Nigri A, Mungieri E, Martuscelli E, et al.. Pulmonary trunk stenosis due to constriction by a pulmonary band. Am Heart J 1987; 114:448-450

10. Nishimura RA, Kazmier FJ, Smith HC, Danielson GK. Right ventricular outflow obstruction caused by constrictive pericardial disease. Am J Cardiol 1985; 55:1447-1448

11. Hancock EW. Subacute effusive constrictive pericarditis. Circulation 1971; 43:183-192

12. Isner JM, Carter BL, Bankoff MS, Kostam MA, Salem DN. Computed tomography in the diagnosis of pericardial heart disease. Ann of Int Med 1982; 97(4):473-479

13. Hancock EW. On elastic and rigid forms of constrictive pericarditis. Am Heart J 1980; 100(6):917-923

14. Meyer TE, Sareli P, Marcus RH, et al. Mechanisms underlying kussmaul's sign. Am J Cardiol 1989; 64:1069-1072

15. Suwan PK, Potjalongsilp S. Predictors of constrictive pericarditis after tuberculous pericarditis. Br Heart J 1995; 73:187-189

16. McCaughan BC, Schaff HV, Piehler JM, et al. Early and late results of pericardiectomy for constrictive pericarditis. J Thorac Cardiovasc Surg 1985; 89:340-350

17. Levine HD. Myocardial fibrosis in constrictive pericarditis. Electrocardiographic and pathologic observations. Circulation 1973; 48:1268-1281

18. Suchet IB, Horwitz TA. CT in tuberculous constrictive pericarditis. J of Comput Assisted Tomogr 1992; 16(3):391-400

19. Schnittinger, I. Pericardial thickening and constrictive pericarditis. Am J Cardiol 1978; 42:388-395

20. Mertens L, Denef B, De Geest H. The differentiation between restrictive cardiomyopathy and constrictive pericarditis: The impact of the imaging techniques. Echocardiography 1993; 10(5):497-508

21. Appleton CP, Hatle LK, Popp RL. Demonstration of restrictive ventricular physiology by doppler echocardiography. J Am Coll Cardiol 1988; 11:757-768

22. Hatle LK, Appleton CP, Popp RL. Differentiation of constrictive pericarditis and restrictive cardiomyopathy by doppler echocardiography. Circulation 1989; 79:357-370

23. Mancuso L, D'Agostino AD, Pitrolo F, et al.. Constrictive pericarditis versus restrictive cardiomyopathy: The role of doppler echocardiography in differential diagnosis. Intl J of Cardiol 1991; 31:319-328

24. Klodas E, Nishimura RA, Appleton CP, Redfield MM, Oh JK. Doppler evaluation of patients with constrictive pericarditis: Use of tricuspid regurgitation velocity curves to determine enhanced ventricular interaction. J Am Coll Caridol 1996; 28:652-657

25. Hurrell DG, Nishimura RA, Higano ST, Appleton CP, Danielson GK, Holmes DR, Tajik AJ. Value of dynamic respiratory changes in left and right ventricular pressures for the diagnosis of constrictive pericarditis. Circulation 1996; 93:2007-2013

26. Vaitkus PT, Kussmaul WG. Constrictive pericarditis versus restrictive cardiomyopathy: A reappraisal and update of diagnostic criteria. Am Heart J 1991; 122(5):1431-1441

27. Schoenfeld MH. The differentiation of restrictive cardiomyopathy from constrictive pericarditis. Cardiology Clinics 1990; 8(4):663-671

28. Hoit B. Pericardial heart disease. Current Problems in Cardiology 1997; 22(7):353-404

29 Oh JK, Tajik J, Appleton CP, Hatle LK, Nishimura RA, Seward JB. Preload reduction to unmask the characteristic doppler features of contrictive pericarditis. Circulation 1997; 95:796-799

30. Bush CA, Stang JM, Wooley CF, Kilman JW. Occult constrictive pericardial disease. Diagnosis by rapid volume expansion and correction by pericardiectomy. Circulation 1977; 56:924-930

31. Hartell GG, Hughes LA, Ko JP, Cohen MC. Magnetic resonance imaging of pericardial constriction: Comparison of cine MR angiography and spin echo technologies. Clinical Radiology 1996; 51:268-72

32. Sechtem RL, Tscholakoff D, Higgins CB. MRI of the normal pericardium. Am J Roentgenology 1986; 147:239-244

33. Masui T, Finck S, Higgins CB. Constrictive pericarditis and restrictive cardiomyopathy: Evaluation with MR imaging. Radiology 1992; 182:369-373

34. Stark DD, Higgins CB, Lanzer P, et al. Magnetic resonance imaging of the pericardium. Normal and pathologic findings. Radiology 1984; 150:469-474

35. Soulen RL, Stark DD, Higgins CB. Magnetic resonance imaging of constrictive pericardial disease. Am J Cardiol 1985; 55:480-484

36. Kushwaha SS, Fallon JT, Fuster V. Restrictive cardiomyopathy. NEJM 1997; 336(4):267-276

37. Copeland JG, Stinson EB, Griepp RB, Shumway NE. Surgical treatment of chronic constrictive pericarditis using cardiopulmonary bypass. J Thoracic Cardiovasc Surg 1975; 69:236

38. Trotter MC, Chang KC, Ochsner JL, McFadden PM. Pericardiectomy for pericardial constriction. The American Surgeon 1996; 62:304-307

Topics in Primary Care Medicine

Low-Molecular-Weight Heparin in the Treatment of Deep Venous Thrombosis

KAREN E. HAUER, MD, *San Francisco, California*

Traditionally, acute deep venous thrombosis (DVT) is treated with intravenous heparin followed by oral anticoagulants. With the advent of the low-molecular-weight heparins (LMWHs), this strategy is changing dramatically. LMWHs are compounds derived from standard unfractionated heparin that offer distinct clinical advantages over unfractionated heparin, including better bioavailability, longer half-life, and a more predictable anticoagulant response that obviates the need for laboratory monitoring. The common side effects of unfractionated heparin, including bleeding, thrombocytopenia, and osteoporosis, may be less common with LMWH. For the treatment of established venous thromboembolism, LMWH is at least as safe and effective as unfractionated heparin. Recent studies demonstrate that home therapy of DVT with LMWH, compared with inpatient therapy with unfractionated heparin, produces comparable clinical outcomes and patient satisfaction, with dramatic cost savings. With careful patient selection, home therapy of venous thromboembolism is quickly becoming the new standard of care.

(Hauer KE: Low-molecular-weight heparin in the treatment of deep venous thrombosis. West J Med 1998 169:240–244)

An estimated 300,000 to 600,000 cases of deep venous thrombosis (DVT) occur annually in the US.[1] Traditionally, therapy has consisted of 5 days of intravenous heparin in the hospital, initiation of oral anticoagulation in the hospital, and continuation of oral anticoagulation for approximately 3 months. This therapy is not without risk, as unfractionated heparin is associated with major bleeding complications in at least 5% of patients.[2] In addition, the cost and duration of hospitalization are increasingly under scrutiny. Therefore, an alternative to unfractionated heparin—one at least as effective and safe as well as less expensive—is highly desirable. The low-molecular-weight heparins (LMWHs) meet these criteria based on data from recent randomized controlled trials.

Biology

Commercial heparin, which is usually extracted from bovine lung or porcine intestinal mucosa, is a heterogeneous mixture of polysaccharides of variable length, ranging in molecular weight from 5 to 30 kDa (mean 12 kDa). LMWH is derived from unfractionated heparin by a process of depolymerization or fractionation. While the molecular weight of unfractionated heparin varies widely, LMWH molecules have molecular weights ranging from 2 to 10 kDa (mean 4–6 kDa) depending on the LMWH preparation (Table 1).

Mechanism of Action

Heparin binds to antithrombin III (AT III), a plasma protein that normally inhibits activated factors II, IX, X, XI, and XII. Heparin contains a unique pentasaccharide with a high-affinity binding sequence to AT III. Factor II (thrombin) and activated factor X (factor Xa) are most sensitive to inhibition by heparin.[2]

Heparin molecules of higher molecular weight inhibit thrombin and factor Xa by different binding mechanisms. To inhibit thrombin, heparin serves as a template to which AT III and thrombin bind, forming a ternary complex. In contrast, factor Xa is inhibited by heparin and AT III without formation of a ternary complex.[3] LMWH molecules less than 5.4 kDa are unable to bind thrombin and AT III simultaneously to form the ternary complex necessary for thrombin inhibition, but all LMWH fragments contain the high-affinity pentasaccharide that binds to AT III and inhibits factor Xa.

At high doses, the anticoagulant effect of unfractionated heparin is also mediated by heparin cofactor II, a naturally occurring plasma protein that inhibits thrombin.[4] Because binding to heparin cofactor II requires a minimum fragment weight of 7.2 kDa, few LMWH fragments bind it at any dose. Thus at high doses, unfractionated heparin has a disproportionate increase in anticoagulant activity not seen with LMWH (Table 1).

From the Division of General Internal Medicine, School of Medicine, University of California, San Francisco.
Reprint requests to Karen E. Hauer, MD, 400 Parnassus Ave, A-405, San Francisco, CA 94143-0320.

ABBREVIATIONS USED IN TEXT

APTT = activated prothrombin time
AT III = antithrombin III
DVT = deep venous thrombosis
FDA = Food and Drug Administration
HIT = heparin-induced thrombocytopenia
INR = international normalized ratio
LMWH = low-molecular-weight heparin

LMWH Preparations

Many LMWH preparations are in clinical use, mainly in Europe and Canada, and three are approved for use in the US (Table 2). The first available in the US was enoxaparin, approved by the Food and Drug Administration (FDA) in 1993 for prophylactic use after total hip replacement surgery. Dalteparin and ardeparin have since been approved, also for prophylactic use.

The higher the molecular weight of the heparin molecule, the greater the anti-thrombin activity. Differences in heparin preparations are expressed in terms of the anti–factor Xa to anti-thrombin activity ratio; by definition, unfractionated heparin has a ratio of 1:1. LMWH preparations have ratios of 2:1 to 4:1.[5] Because each LMWH preparation has a different ratio, data regarding one LMWH cannot be assumed to apply to the others. A better measure of LMWH anticoagulant activity than the activated prothrombin time (APTT) is the anti-Xa activity, which can be measured in many laboratories. The differences among LMWH preparations may not translate into differences in clinical efficacy or side effects when the drugs are dosed according to anti-Xa activity.

Advantages of LMWH

LMWH has several advantages over unfractionated heparin (Table 3), both pharmacokinetic (what the body does to absorb and metabolize the drug) and pharmacodynamic (what the drug does to the body).

Longer Half-Life

The half-life of unfractionated heparin after subcutaneous injection is 1 to 2 hours; after intravenous injection, it varies according to dose. The half-life of LMWH is two to four times longer, up to 6 hours. This extended action allows LMWHs to be administered once or twice daily for a sustained 24-hour effect.

Less Variability in Anticoagulant Response

LMWH provides predictable anticoagulant effects without need for routine APTT monitoring. Although some LMWHs require initial dose adjustment for body weight, others do not, particularly at prophylactic doses in adults. In some situations, including obesity, renal failure, and pregnancy, the response to LMWH can be variable; in those cases, anti-Xa activity should be monitored.

In contrast, the response to unfractionated heparin varies, for several reasons. The dose-response relationship is not linear: increasing doses of unfractionated heparin produce disproportionate increases in half life. Unfractionated heparin binds to endothelial cells and macrophages until these sites are saturated and then is cleared by renal excretion. (LMWH is cleared mainly by renal excretion at any dose, and the clearance is prolonged in patients with renal failure.[6]) Unfractionated heparin also binds to many plasma proteins that neutralize its action, including platelet factor 4, histadine-rich glycoprotein, and vitronectin.[7] Because many of those proteins are acute-phase reactants, the bioavailability of unfractionated heparin is frequently altered. (With the exception of AT III, LMWH does not bind to plasma proteins and thus produces a more predictable anticoagulant effect.)

Better Availability After Subcutaneous Injection

The onset of action of unfractionated heparin is delayed 1 to 2 hours after subcutaneous injection; LMWH has an immediate onset of action. The binding of unfractionated heparin to plasma proteins leads to decreased bioavailability and delayed activity at low concentrations until those protein sites are saturated.

Potentially More Favorable Antithrombotic to Hemorrhagic Ratio

Unfractionated heparin has an inhibitory effect on platelets and increases vascular permeability; LMWH does not.[6] These in vitro differences possibly translate into less clinical bleeding.

Less Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is characterized by a ≥50% reduction in platelet count between 5 and 15 days after initiation of full- or low-dose heparin ther-

TABLE 1.— *Differences Between Unfractionated Heparin and LMWH*

	Unfractionated heparin	*LMWH*
Source	Bovine lung or porcine intestinal mucosa	Depolymerization of unfractionated heparin
Molecular weight of fragments (kDa)	5–30	2–10
Inhibition of thrombin	Forms ternary complex with AT III and thrombin	Fragments <5.4 kDa do not form ternary complex
Anti–factor Xa to anti-thrombin activity ratio	1:1	2:1 to 4:1
Binding to heparin cofactor II	fragments >7.2 kDa bind at high dose	Few fragments bind at any dose

TABLE 2.—*FDA-Approved LMWH Preparations*

LMWH and manufacturer	*Molecular weight (mean kDo [range])*	*Indications for use*	*Subcutaneous dose*	*Cost per day*
Enoxaparin (Lovenox)	4.5 (3–8)	Prophylaxis: hip/knee replacement	30 mg bid	$35.38
		Prophylaxis: extended hip	40 mg qd	$23.52
		Abdominal surgery	40 mg qd	$23.52
		Treatment of unstable angina and non–Q wave MI*	1 mg/kg bid	$47.04†
Dalteparin (Fragmin)	5 (2–9)	Prophylaxis: abdominal surgery	2500 anti-Xa U qd	$13.95
		Treatment*	200 U/kg qd	—
Ardeparin (Normiflo)	6	Prophylaxis: knee surgery	50 anti-Xa U/kg bid	$30.90‡
Heparin (various manufacturers)	5–30	Prophylaxis	5000 U bid	~$1–2
		Treatment	~24,000 U/d (weight based)	~$2–4

Source: Drug Topics Red Book, 1998.

*Unlabelled use: other therapy of arterial and venous thromboembolism.
†For patient weighing 80 kg.
‡For patients weighing up to 100 kg.

apy.[8] HIT type I consists of an early asymptomatic decline in platelet count; patients with HIT type II develop thrombocytopenia with thrombotic complications (arterial, venous, or both).[9] Thrombotic complications are particularly difficult to treat, primarily because of the paucity of alternatives. The mechanism of HIT type II appears to be immunologically mediated, with formation of immunoglobulins that bind complexes of heparin and platelet factor 4 via the platelet Fc receptor, leading to platelet aggregation.[10] In patients receiving heparin, platelet counts should be monitored daily for development of HIT. Thrombocytopenia typically resolves within 1 week of discontinuing heparin therapy.[11]

Unfractionated heparin derived from bovine lung more frequently causes thrombocytopenia than that derived from porcine gut, and LMWH is less likely to cause thrombocytopenia than either. Warkentin et al.[12] compared the rates of thrombocytopenia in 665 patients receiving prophylaxis after hip surgery with either 7500 U unfractionated heparin SQ bid or 30 U enoxaparin SQ bid. Nine patients (2.7%) in the unfractionated heparin group developed thrombocytopenia, vs. zero in the LMWH group. Importantly, eight of the nine patients (89%) with HIT had thrombotic events; only 18% of patients without HIT developed thromboses during the study period. A random subset of the total study population was tested for heparin-dependent immunoglobulin antibodies. Of the 387 screened patients, 7.8% receiving unfractionated heparin tested positive vs. 2.2% receiving LMWH. Development of antibodies occurred 5 to 10 days postoperatively and was associated with thromboses only in patients who also became thrombocytopenic.

Although the risk of HIT is lower with LMWH than with unfractionated heparin, patients with established HIT have a high rate of cross-reactivity when switched to LMWH because the proposed immunologic reaction is not heparin type–specific; therefore those patients cannot safely receive either preparation.[13] Danaparoid sodium and newer experimental anticoagulants may be successful alternative therapy for some patients with HIT.[14]

Lower Frequency of Heparin-Associated Osteoporosis

Heparin at doses >15,000 U/day for periods over 1 month causes osteoporosis that is dose- and duration-dependent.[15] The mechanism is unclear, but animal studies have demonstrated decreased bone formation and increased resorption with unfractionated heparin.[16] The only randomized trial evaluating the risk of heparin-induced osteoporosis with long-term unfractionated heparin vs. LMWH in humans demonstrated a lower rate of spinal fracture in the LMWH-treated patients.[17]

Treatment of DVT

Conventional initial treatment of acute DVT has consisted of IV heparin for 5 to 7days in the hospital, with a goal APTT of 1.5 to 2 times normal.[18,19] Coumadin is started on day 1 with a goal international normalized ratio (INR) of 2 to 3. With this regimen, the 3-month thrombus recurrence rate is about 5 to 7%.[2] Subcutaneous unfractionated heparin is equally effective to that delivered intravenously if the APTT is checked frequently to maintain it in the therapeutic range; some authorities recommend an initial intravenous bolus before subcutaneous therapy to overcome the delayed action after subcutaneous injection.[11] The risk of major bleeding during initial heparin treatment is about 5% (range 1–33%), depending on dose, method of administration, and the patient's other risk factors for bleeding.[2]

TABLE 3.—*Advantages of LMWH Over Unfractionated Heparin*

Longer half-life
Less variability in anticoagulant response—no need to monitor APTT
Better bioavailability after subcutaneous injection
Fewer cases of heparin-induced thrombocytopenia
Fewer cases of heparin-induced osteoporosis

TABLE 4.—*Home Therapy of DVT with LMWH*

	Unfractionated heparin	*LMWH*
Recurrent thromboembolism (%)		
Levine[20] (3 months)	6.7	5.3
Koopman[21] (6 months)	8.6	6.9
Major bleeding on heparin (%)		
Levine[20]	2.0	1.2
Koopman[21]	1.0	0.5
Mean length of stay in hospital (days)		
Levine[20]	6.5	1.1
Koopman[21]	8.1	2.7

After multiple studies comparing LMWH to unfractionated heparin for treatment of DVT in hospitalized patients, two 1996 studies[20,21] examined the efficacy, safety, and feasibility of outpatient treatment of acute DVT (Table 4). Levine et al.[20] randomly assigned 500 patients with acute proximal DVT to receive either intravenous unfractionated heparin or 1 mg/kg enoxaparin SQ bid as initial treatment until a therapeutic INR was established with coumadin.[20] Study endpoints were symptomatic recurrence by 3 months and bleeding on heparin therapy. Two-thirds of the 2230 patients originally screened were ineligible for home therapy because of comorbidities, concurrent symptomatic pulmonary embolism, history of two or more prior DVTs or pulmonary embolisms, or other reasons. Of the 739 eligible patients, 500 (68%) agreed to participate. Results showed a recurrence rate of 5.3% in the LMWH group vs. 6.7% in the unfractionated heparin group (95% CI –3.0 to 5.7). The mean hospital stay for the LMWH group was 1.1 days vs. 6.5 days in the unfractionated heparin group.

In a companion paper, Koopman et al.[21] compared another LMWH, nadroparin, administered subcutaneously on a weight-adjusted basis with intravenous unfractionated heparin in 400 patients in Europe and Australia.[21] The 6-month DVT recurrence rate was 6.9% in the nadroparin group vs. 8.6% in the unfractionated heparin group (95% CI –3.6 to 6.9). Despite the inclusion of patients who were not able to receive home therapy, 36% in the nadroparin group were never admitted and 40% were discharged early: the average hospital stay was 2.7 days in the LMWH group vs. 8.1 in the unfractionated heparin group, a 67% reduction. Quality of life as assessed by questionnaires was similar in the two groups except for significantly better physical activity and social functioning scores over time in the LMWH group. In both studies, there was a nonsignificant trend toward decreased bleeding complications with LMWH.

Although never assessed in a randomized prospective trial, the potential cost savings associated with home therapy using LMWH were illustrated in a nonrandomized study of 434 patients treated with 200 U/kg/day subcutaneous dalteparin for acute DVT.[22] The patients were followed prospectively, and costs were compared with historical controls treated with intravenous heparin. Only 19.8% of patients required exclusively inpatient therapy, and 35% were hospitalized for less than 1 day, translating into a 34.5% cost reduction. The main reasons for hospital admission were geography, personal reasons, and comorbidities.

Two large recent studies[23,24] expanded the spectrum of patients eligible for LMWH therapy of venous thromboembolism by including patients with pulmonary embolism, cancer, or prior thromboembolism. The Columbus Investigators[23] randomly assigned 1021 patients with venous thromboembolism, including 26% with pulmonary embolism at presentation, to LMWH or unfractionated heparin. Rates of recurrent thromboembolism and major bleeding over 12 weeks were equivalent, and 42% of DVT patients in the LMWH group were discharged early to be treated at least partially at home. In contrast, Simonneau et al.[24] compared LMWH to unfractionated heparin in 612 hospitalized patients, all with acute symptomatic pulmonary embolism, using a combined endpoint of symptomatic recurrent thromboembolism, major bleeding, and death at 8 and 90 days. Again, there were no statistically significant differences in any of the measured outcomes. Because 73% of patients in the LMWH group received initial therapy with unfractionated heparin for a mean of 18 hours, the effectiveness of a regimen using exclusively LMWH was not evaluated. In both studies, about half of deaths due to pulmonary embolism occurred within the first week of therapy. These provocative results indicate that LMWH is efficacious in the treatment of pulmonary embolism; they do not fully answer the questions of safety or cost-effectiveness of home therapy of pulmonary embolism or guide clinicians in identifying patients at low risk of hemodynamic compromise who may safely be treated at home.

Conclusions

LMWH is an alternative to unfractionated heparin for the treatment of DVT that offers multiple pharmacologic and clinical advantages. Two randomized controlled trials have demonstrated the efficacy and feasibility of home treatment of acute DVT with LMWH, suggesting that at least one-third of patients may be eligible to receive all of their therapy outside the hospital. A cost analysis has quantified the dramatic savings derived from avoiding hospitalization. In addition, LMWH is more convenient for patients because, in most cases, no laboratory monitoring is required.

Are the available data sufficient to choose a heparin preparation to treat acute thromboembolism? With multiple studies showing that the efficacy of unfractionated heparin and LMWH are equivalent, clinicians and policy makers have been actively evaluating whether the pharmacologic advantages of LMWH justify its higher cost to produce. (Conversely, if the high price of producing LMWH decreases over time, the overall cost savings will increase further.) The benefits of LMWH ther-

apy that make it the currently emerging standard of care are cost-effectiveness and convenience. The largest savings with LMWH result from a decrease in hospitalization time; hospital care comprises the greatest proportion of health care expenditures in the US, and methods of care which obviate the need for hospitalization lower the cost of health care (unless the alternatives are more expensive, resulting in cost shifting).[25] Although outpatient LMWH therapy requires trained medical personnel to educate patients and monitor outpatient care, these expenses do not exceed the cost of inpatient care. Cost analyses of LMWH must be scrutinized for bias not only in terms of potential cost shifting to the outpatient setting, but also in terms of the specific dosing regimens compared, the endpoints assessed, and home therapy's impact on quality of life.

For certain groups of patients, including those with obesity or renal failure in whom the dosing of LMWH is unreliable, unfractionated heparin may remain the preferred therapy of venous thromboembolism. Cost differences may be inadequate to justify the use of LMWH in patients requiring hospitalization for other reasons, including hemodynamic compromise from pulmonary embolism, comorbidities, preference, and inability to perform home injections. Patients with a history of HIT should generally be treated with an alternative anticoagulant agent.

Acknowledgments

The author thanks Julie Hambleton, MD, of the University of California, San Francisco, for her expert review of the manuscript.

REFERENCES

1. Consensus Conference: Prevention of venous thrombosis and pulmonary embolism. JAMA 1986; 256:744–749

2. Hirsh J: Heparin. N Engl J Med 1991; 324:1565–1574

3. Schafer AI: Low-molecular-weight heparin —an opportunity for home treatment of venous thrombosis. N Engl J Med 1996; 334:724–725

4. Sie P, Petitou M, Lormeau J, Dupouy D, Boneu B, Choay J: Studies on the structural requirements of heparin for the catalysis of thrombin inhibition by heparin cofactor II. Biochim Biophys Acta 1988; 966:188–195

5. Fareed J, Hoppensteadt DA: Pharmacology of the low-molecular-weight heparins. Semin Thromb Hemost 1996; 22 (Suppl 2):13–18

6. Green D, Hirsh J, Heit J, Prins M, Davidson B, Lensing AWA: Low molecular weight heparin: a critical analysis of clinical trials. Pharmacol Rev 1994; 46:90–109

7. Lane DA, Pejler G, Flynn AM, Thompson EA, Lindahl U: Neutralization of heparin-related saccharides by histidine-rich glycoprotein and platelet factor 4. J Biol Chem 1986; 261:3980–3986

8. Harenberg J, Huhle G, Piazolo L, Wang LU, Heene DL: Anticoagulation in patients with heparin-induced thrombocytopenia type II. Semin Thromb Hemost 1997; 23:189–196

9. Chong BH, Ismail F: The mechanism of heparin-induced platelet aggregation. Eur J Haematol 1989; 43:245–251

10. Kelton JG, Smith JW, Warkentin TE, Hayward CPM, Denomme GA, Horsewood P: Immunoglobulin G from patients with heparin-induced thrombocytopenia binds to a complex of heparin and platelet factor 4. Blood 1994; 83:3232–3239

11. Hirsh J, Hoak J: Management of deep vein thrombosis and pulmonary embolism. Circulation 1996; 93:2212–2245

12. Warkentin TE, Levine MN, Hirsh J, Horsewood P, Roberts RS, Gent M, et al.: Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. N Engl J Med 1995; 332:1330–1335

13. Greinacher A, Michels I, Mueller-Eckhardt C: Heparin-associated thrombocytopenia: the antibody is not heparin specific. Thromb Haemost 1992; 67:545–549

14. Warkentin TE: Heparin-induced thrombocytopenia: pathogenesis, frequency, avoidance and management. Drug Saf 1997; 17:325–341

15. Griffith GC, Nichols G, Asher JD, Flanagan B: Heparin osteoporosis. JAMA 1965; 193:91–94

16. Muir JM, Hirsh J, Weitz JI, Andrew M, Young E, Shaughnessy SG: A histomorphic comparison of the effects of heparin and low-molecular-weight heparin on cancellous bone in rats. Blood 1997; 89:3236–3242

17. Monreal M, Lafoz E, Olive A, del Rio L, Vedia C: Comparison of subcutaneous unfractionated heparin with a low-molecular-weight heparin (Fragmin) in patients with venous thromboembolism and contraindications to coumarin. Thromb Haemost 1994; 71:7–11

18. Brandjes DPM, Heijboer H, Buller HR, deRijk M, Jagt H, Wouter ten Cate J: Acenocoumarol and heparin compared with acenocoumarol alone in the initial treatment of proximal-vein thrombosis. N Engl J Med 1992; 327:1485–1489

19. Hull RD, Raskob GE, Rosenbloom D, Panju AA, Brill-Edwards P, Ginsberg JS, et al.: Heparin for 5 days as compared with 10 days in the initial treatment of proximal venous thrombosis. N Engl J Med 1990; 322:1260–1264

20. Levine M, Gent M, Hirsh J, Leclerc J, Anderson D, Weitz J, et al.: A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. N Engl J Med 1996; 334:677–681

21. Koopman MMW, Prandoni P, Piovella F, Ockelford PA, Brandjes DPM, van der Meer J, et al.: Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. N Engl J Med 1996; 334:682–687

22. Lindmarker P, Holmstrom M: Use of low molecular weight heparin (dalteparin), once daily, for the treatment of deep vein thrombosis. A feasibility and health economic study in an outpatient setting. J Intern Med 1996; 240:395–401

23. The Columbus Investigators: Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. N Engl J Med 1997; 337:657–662

24. Simonneau G, Sors H, Charbonnier B, Page Y, Laaban J-P, Azarian R, et al.: A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. N Engl J Med 1997; 337:663–669

25. Levit KR, Lazenby HC, Sivarajan L: Health care spending in 1994: slowest in decades. Health Aff 1996; 15:130–144

Topics in Primary Care Medicine

Primary Care for Those With Severe and Persistent Mental Illness

CYNTHIA CREWS, MD, HOLLY BATAL, MD, TOM ELASY, MD, EDMUND CASPER, MD, *and* PHILIP S. MEHLER, MD,
Denver, Colorado

Historically, the medical care of persons with severe and persistent mental illness (SPMI) has been suboptimal. In many communities, large gaps exist in the continuum of services necessary to meet the medical needs of those patients, and existing services are not well coordinated. The effect of the managed mental health care on patients with SPMI remains to be seen, but it does not bode well for patients who are already at risk for being undertreated. We initiated primary care clinics exclusively for patients with SPMI because of our belief that integrating primary care and mental health services offers the best hope of improving health care for those patients. Our experience to date is instructive for other health care systems.

(Crews C, Batal H, Elasy T, Casper E, Mehler PS: Primary care for those with severe and persistent mental illness. West J Med 1998; 169:245–250)

The deinstitutionalization of people with severe and persistent mental illness (SPMI) has resulted in a shift of the burden of care from state hospitals to communities. Before 1955, patients with severe mental illnesses were cared for in a semipermanent manner by public mental hospitals that provided food, shelter, and ongoing medical care. The move toward community care has resulted in deficiencies in housing and basic medical care for SPMI patients.[1] Because of the large gaps that exist in the continuum of services necessary to meet the needs of the severely mentally ill, there is a tendency for these patients to "slip through the cracks" and end up in jails, in shelters, or on the streets.[2] These circumstances, in concert with the perception that patients with concomitant mental illnesses increase health care costs,[3] provide a compelling incentive to devise more effective strategies to care for them.

Despite evidence of high rates of medical comorbidity,[4–8] many patients with severe mental illness do not receive ongoing medical care; rather, they receive care sporadically and at late stages of disease. When patients do seek care in the mental health setting, medical comorbidity is frequently unrecognized,[9,10] leading to higher rates of morbidity and mortality.[11] In addition, substance abuse is prevalent in this population[12] and has been correlated with serious medical sequelae and an increased need for acute inpatient treatment.[13,14]

Many complex factors lead to the breakdown in delivery of care to patients with SPMI. They involve characteristics inherent to this population, including paranoia and psychosis, as well as characteristics of medical care professionals and health care systems themselves. The absence of a regular source of health care results in worse overall health outcomes,[15] so the numerous impediments to providing proper care for these patients must be removed.

Just as primary care patients are reluctant to accept referrals to mental health specialty settings,[16] the chronically mentally ill seldom receive quality primary care.[17] A mortality rate four times that of the baseline population was recently reported in the homeless population,[18] a group with a high incidence of chronic mental illness. Without an ongoing formalized structure or a strong relationship with primary medical care givers, those patients are at risk for noncompliance and rapid decompensations in clinical status.

Historically, there has been a separation of psychiatry from general medical care. The prevailing understanding of disease processes is one that promotes a mind-body dualism, which in turn fosters the separation of the general medical and mental health domains of care.[19] Similarly, there has been a paucity of effort directed toward initiating and securing a strong relationship between primary care and psychiatry for treating the medical problems of patients with chronic mental illness.[20] Although some recent discussions and proposals within the field of psychiatry have focused on bridging the gap between psychiatry and primary care,[21] they have mostly addressed the detection and treatment of psychiatric disorders in a primary care setting[22] or the training of psy-

From the University of Colorado Health Sciences Center (Drs Crews, Batal, Elasy, and Mehler) and the Division of General Internal Medicine (Drs Crews, Batal, Elasy, and Mehler) and Psychiatric Services (Dr Casper) at Denver Health Medical Center, Denver, Colorado.

Reprint requests to Philip S Mehler, MD, Denver Health Medical Center, 777 Bannock Street, MC1914, Denver, CO 80204 (e-mail: pmehler@dhha.org).

ABBREVIATIONS USED IN TEXT
MHCD = Mental Health Corporation of Denver
SPMI = severe and persistent mental illness

chiatrists to also function as primary care physicians for simple internal medicine problems. Providing quality primary care for patients with SPMI is a separate and unknown clinical area. Therefore, it was our goal to improve medical care for SPMI patients by developing clinics, staffed by internists, that provide primary care exclusively for such patients. We opted for this type of health care delivery model because we believe that the high medical comorbidity found in this patient population is best served by internists. The SPMI patient needs a physician trained in the complex spectrum of primary care internal medicine.

Discussion between psychiatry and general internal medicine at Denver Health Medical Center identified the SPMI patient group as one that lacked continuity of medical care. Psychiatrists frequently noted untreated medical conditions upon presentation for psychiatric emergency services or admission to the psychiatric inpatient service. Internists observed that individuals with psychiatric disorders often inappropriately visited the urgent care clinic and emergency department. Both physician groups believed that a lack of continuity led directly to reliance on the more expensive and sporadic treatment provided through urgent and emergent services. We believed that designating clinics and physicians for this patient group would provide better patient adherence and access to primary medical care. The underlying theme of this experiment was predicated on the compelling belief that consistent and well organized treatment of chronic conditions will reduce the need for acute costly episodic services, will prevent disease progression, and will improve the overall health of those with severe and persistent mental illness.

Methods

In collaboration with the Mental Health Corporation of Denver (MHCD), the designated provider of all publicly funded outpatient mental health services for the city and county of Denver, we at Denver Health Medical Center initiated a program that serves SPMI patients in the setting of a primary care clinic.[23] Denver Health Medical Center is an integrated health care system that includes an acute care hospital and 10 community health centers located in medically underserved areas throughout Denver County. This system of hospital and clinics is integrated under one administration and a single system of medical records. Denver Health Medical Center provides approximately 40% of the unreimbursed care for the state of Colorado.

The MHCD provides comprehensive outpatient mental health care including psychiatric evaluation, medication prescription and monitoring, case management, housing programs, crisis intervention, and community outreach programs. Services are provided to clients at more than 30 locations throughout Denver, and clients are billed for services based on their ability to pay. Approximately 80% of MHCD patients are covered by Medicaid or Medicare. The MHCD serves 3600 adult clients, the majority of whom carry an axis I diagnosis of schizophrenia or severe affective disorder. These patients are of mixed ethnicity (51% white, 24% Hispanic, 21% African-American) and are almost exclusively indigent, 90% having incomes less than $10,000 per year.

To provide primary care to this population, two clinics were set up in the Community Health Department: one in the ambulatory care clinic of Denver Health proper and the other at Eastside Family Health Center, one of the Denver Health community-based neighborhood clinics. Each clinic operates one half-day a week and is staffed by a board-certified general internist. Physicians were selected for their willingness to work with this group of patients. Given that they had not received additional formal psychiatric training, their involvement and interest in this population self-directed their efforts to expand their knowledge.

Substantial time was spent designing and refining the proper referral system to support and improve collaboration between the separate medical and mental health care systems. After much deliberation, we decided that referrals to the clinics would be made by professional staff at MHCD by completing a standard form *before* the patient's first appointment. This form provided basic psychiatric and medical information, a current medication list, demographic details such as present housing situation, and telephone contact numbers for case managers and physicians at the MHCD. We decided the case managers would be the best to initially elicit this important information because of their established rapport with these patients. The referral also specified any symptoms or medical complaints requiring evaluation and treatment. Likewise, a completed treatment plan was communicated to the MHCD staff after each appointment in primary care.

Results

Before the clinics' inception, we tested our assumptions regarding patterns of health usage and access in this population by conducting a random survey of 100 MHCD patients (although we did not use a formal, validated survey tool). The results showed that a significant number of these patients are not linked to ongoing primary care: 61% reported that they would go to the emergency department or urgent care clinic if they felt sick; only 20% said they would see their "regular physician." Fifty percent reported having a regular doctor, and only 50% of those patients said their regular physician was an internist/family doctor. The others reported their regular physician to be a psychiatrist or were unsure.

During the first 6 months of the trial, 220 patients (unduplicated visits) were seen at the clinics. Patients were 59% male; 53% age 26–44 years and 38% 45–65;

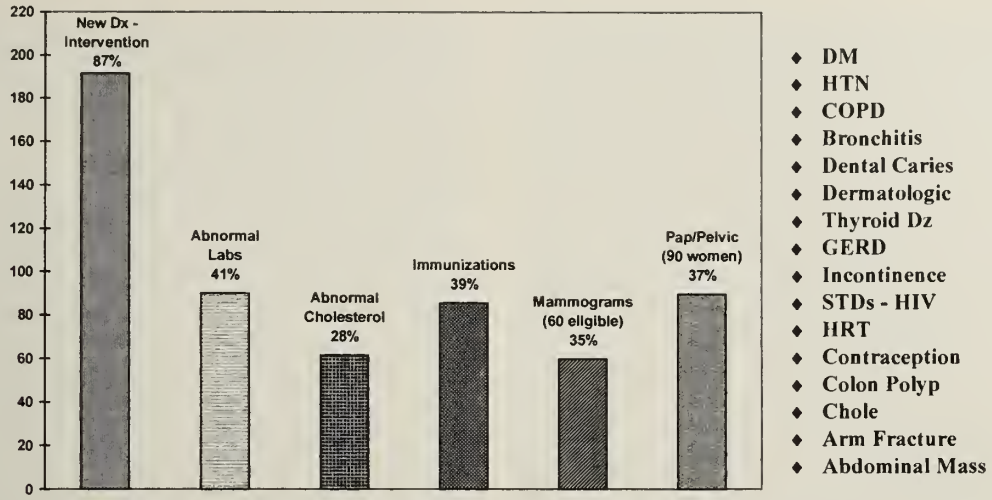


Figure 1.—Clinical results of 220 chronically mentally ill patients in primary care clinics.

66% white, 18% African-American, and 14% Hispanic. Sixty-one percent were schizophrenic, 20% were bipolar, and 14% carried a diagnosis of major depression. As expected, few patients referred were under age 26 or over age 65. (It is likely that younger persons with severe mental illness are not yet dependent on the public health and mental health care systems and are perceived to have less need for ongoing medical care, while persons over age 65 actually have more resources for health care due to entitlement programs for the elderly.) Seventy-eight percent of the patients smoked, 24% more than two packs per day. Forty-four percent reported a history of alcohol abuse, and 31% reported a history of other substance abuse.

In 191 patients (87%), we were able to make a new diagnosis or intervention (Figure 1). Diagnoses ranged from basic infections, abnormal Pap smears, hypertension, and new-onset diabetes mellitus to a previously unrecognized upper extremity fracture that required immediate hospitalization.

We stressed preventive health measures: we updated immunizations in 39% of the 220 patients and performed mammograms in 35% and Pap smears in 37% of eligible women. With the exception of thyroid-stimulating hormone and cholesterol, screening labs done in asymptomatic patients during this pilot project (complete blood count, chemistry panels, and serological tests for syphilis, HIV, and hepatitis) generally were normal and did not influence management.

Discussion

Our clinical results are consistent with literature describing high rates of medical comorbidity and substance abuse in the severely mentally ill.[5,13,24–26] Chronically mentally ill adults have traditionally accounted for a large portion of health care expenditures.[27] Without adequately established primary care programs, they tend to access care through emergency departments and urgent care clinics where the cost of care is more expensive.[28] Several factors contribute: a lack of regular medical care results in a deterioration of the individual's health to a point where urgent care becomes necessary; alternatively, if patients lack access to primary care, they are likely to seek care from a site where access is less impeded such as an emergency department or urgent care clinic. This pattern of utilization was observed by the Medicaid access group who found that Medicaid recipients in urban areas have extremely limited access to outpatient care apart from that offered in hospital emergency rooms.[29] Surveys of Medicaid recipients who are not necessarily mentally ill reveal that more than 60% had no regular source of care.[30] In addition, patients who are unaffiliated with a primary care physician are known to visit the emergency room repeatedly.[31] Merely putting forth efforts to limit these emergency room visits, when established alternative sources of care are lacking, will be fraught with problems.[32] These conclusions seem especially applicable to SPMI patients because their concurrent mental illness typically causes them to have increased difficulties in dealing with the health-care system.

Although it is too early to allow for an analysis of the economic impact of the clinic, from an initial overview of clinic attendance, the high rate of kept appointments, and the nature of medical conditions treated, we believe the economic impact will be positive over time. While this is open to discussion,[33] from an intuitive standpoint, enhancing the role of primary care for an underserved population should help moderate health care costs. Many of these same patients are indigent and thus served in the public sector. If we as a society and medical community do not invest the necessary time and effort to address the health needs of SPMI patients, we will inevitably be faced with having to pay for the additional health care costs for problems once they progress. Managing the care of chronically mentally ill patients may be one important strategy for health care agencies

hoping to eliminate the excessive costs of unnecessary emergency room visits. Similarly, the traditional emergency department and urgent care clinic visits for these patients are inefficient. The marginal costs of emergency care for non-emergent conditions are more expensive than an office visit;[34] even if this difference is relatively small, limiting these costs is a worthwhile goal.

However, the economic argument does not tell the entire story. An accurate cost analysis must also include the costs of failure to prevent additional medical sequelae, as well as the lost opportunity to form an ongoing relationship that promotes further evaluation, long-term management, and health education of the patient. As an example, a patient with emphysema in an ongoing primary care setting can be taught about avoiding triggers for respiratory deterioration, preventive care through influenza and pneumococcal immunization, and symptom monitoring during flares of the disease. There is seldom adequate time for patient education during an urgent care visit.

In the long run, the effectiveness of primary care in this population will be assessed based on the patients' health outcomes. The continuity we are striving to achieve for these traditionally problematic patients has in other populations been linked to improved outcomes.[35] Having a regular place of care has been shown to be the most important factor associated with receiving preventive care services.[36] The SPMI patient often places a low priority on these types of services because of more pressing psychological or social stresses or because of a lack of understanding of the benefits. We believe that the ability to perform routine health maintenance will continue to increase as patients become more comfortable and trusting of the clinics and those who provide their care. Currently, no literature addresses the utilization patterns of preventive services by this patient population. Often we have found that in contrast with other patients in a general internal medicine clinic, SPMI patients require more extensive explanations about the need for screening examinations and laboratory work. An incremental approach has been successful in many patients—early visits involve screening procedures that are the least intrusive and more sensitive tests are done at later visits when the patient feels more comfortable.

Because of their inherent paranoia, SPMI patients are more likely to return for follow-up and adhere to treatment plans if they trust the health care staff. Early on, when ancillary clinic staff expressed some hesitancy about caring for this population, we developed a number of educational sessions to discuss salient aspects of chronic mental illness in order to encourage a better understanding and empathy. In addition, the selection of primary care physicians is crucial to the success of such a clinic. The physicians must be adept at creating an atmosphere of respect and trust for the patients. This ability of the primary care physicians and support staff to build a strong relationship with the patient may prove to be the most significant variable in the success or failure of this type of clinic. Thus, on occasion, the obvious treatment regimen for a particular medical problem has to be put in abeyance because it may provoke fear and destroy the developing relationship that is necessary to provide ongoing treatment.

Inconsistent follow-up and difficulties with treatment plan adherence have commonly been found in this population. Our finding, that SPMI patients often lack primary care physicians, is consistent with earlier studies and likely has a role in this problem.[37] The chronically mentally ill are at a major disadvantage in dealing with health care systems; barriers to optimal primary care have been elucidated.[38] Many patients are aggressive, volatile, and noncompliant while lacking adaptive skills to function in a system where access to care may be challenging. They often lack transportation and education, factors which are known to predict delaying or forgoing care for a medical problem.[39] To improve adherence, we have enlisted the collaboration of the patients' case managers, who frequently accompany their clients to clinic appointments. The case managers facilitate access to the clinic by making appointments and transporting the patients. They elaborate on symptomatology, provide information about patients' day-to-day life, reinforce the treatment plan, enhance communication between the medical and psychiatric professionals, and serve as a liaison between patients and their medical care team. Rosenheck et al.[40] recently demonstrated that health services utilization was primarily associated with identification of such a need by the case manager, not the client.

The feedback about the clinics has been uniformly positive. The psychiatry staff at the MHCD appreciate the direct lines of communication that have been established with the primary care physicians and frequently consult the internists by phone. Several psychiatrists have expressed relief that the medical issues of their patients are being addressed in a structured fashion. By establishing clinics that expressly serve this population, we have sought to streamline the medical care for the patients and staff at MHCD. In the past, case managers may have had a different physician for each of their clients; now they are able to find one for a whole cohort of their clients. It is also easier for the mental health team to obtain clients' medical records, laboratory results, medication refills, and same-day appointments for acute illnesses because of the involvement of the case managers. The same-day appointments serve as an alternative to more expensive methods of care such as the urgent care clinic or the emergency room.

Given their precarious nature, SPMI patients require a system that promotes flexibility and creativity to improve the historically high rates of attrition when they are simply provided care in a general office or hospital-based clinic setting.[41] Efforts to integrate primary medical care with mental health care may result in an organizational structure that can add the necessary coherence to the system of services for the chronically mentally ill.[42] It has also been demonstrated that interventions to

improve the quality of health care through case management may be most successful when they focus on selected high-risk populations such as SPMI patients.[43]

The main lesson we have learned is that communication with the psychiatric staff is imperative. The MHCD has the structure to reinforce the treatment plan and, most importantly, the MHCD staff members are the ones who have long-standing relationships with the patients. They have the knowledge of psychiatric medications, which the patients often do not remember, and of the patients' living situations and functional status. A coordinated effort between the internal medicine staff and the psychiatry staff is required.

The main ongoing problems posed by dealing with this population are in the areas of coordination of care, approaches to follow-up, and medication compliance. In addition, patients are skeptical about some treatments, especially preventive services that do not have immediately obvious results, and they are often on so many medications that they refuse additional ones. Both these problems are most successfully dealt with by scheduling frequent follow-up visits to reinforce the treatment plan and forge trust. Education of the case managers and psychiatrists about the need for a specific treatment allows for reinforcement in a more natural and less threatening environment outside of the primary care clinic. The structure is often in place to fill "medi-planners" during psychiatric visits, and the psychiatric staff now incorporate medications for medical problems into the planners.

Transportation to the clinic is difficult. Unless the patient is being intensively case managed and is provided transportation, he or she may miss the appointment. Just communicating with the clinic can be difficult—patients often do not have phones and become frustrated and confused with the process. Another problem involves differentiating between somatic manifestations of psychiatric illness and medical illness, which requires multiple visits and carefully focused evaluation and testing to rule out serious illness. Finally, psychiatric medications cause a large number of side effects. It may be difficult to decide when to recommend a switch of medications, especially when the medication is successful psychiatrically but complicates the medical health picture, or in patients who have unsuccessfully tried numerous psychotropic medications in the past.

Important questions to consider: 1) Can this clinic be replicated with any physician? 2) How might primary care physicians be better trained to provide appropriate care for SPMI patients? 3) What specific skills, knowledge, and experience are necessary to take care of SPMI patients?

The clinic can be replicated if the necessary infrastructure for the clinic is available and communication pathways are arranged between the psychiatry and internal medicine divisions. Medical personnel need psychiatric back-up and resources (such as social workers) for the less independent patients. Primary care physicians need a basic understanding of the psychiatric illnesses, psychotropic medication indications, and side effects. Mostly, they need patience and empathy.

Ultimately, we intend to evaluate the cost-effectiveness of these clinics based on the medical and psychiatric outcomes through a randomized prospective trial. Patient and doctor satisfaction with the primary care clinics is another area to explore. We believe the results of these analyses will support our hypothesis that the basis for improved health care in the patient with SPMI will continue to rest on the establishment of a secure ongoing relationship between psychiatric staff, patients, and a primary care physician. Medical clinics developed exclusively for severely mentally ill patients may be the ideal way to care for them.[44]

REFERENCES

1. Susser E, Valencia E, Conover S, Felix A, Tsai W, Wyatt RJ. Preventing recurrent homelessness among mentally ill men: A "critical time" intervention after discharge from a shelter. Am J Public Health 1997; 87:256–262

2. Torrey EF. Jail and prisons—America's new mental hospitals. Am J Public Health 1995; 85:1611–1613

3. Novack DH, Goldberg RJ. Psychiatric problems in primary care. J Gen Intern Med 1996; 11:56–57

4. Roca RR, Breakley WR, Fischer PJ. Medical care of chronic psychiatric outpatients. Hosp Comm Psychiatry 1987; 38:74–75

5. McCarrick AK, Manderscheid RW, Bertolucci DE. Chronic medical problems in the chronically mentally ill. Hosp Comm Psychiatry 1986; 37:289–291

6. Tsuang M, Perkins K, Simpson J. Physical diseases in schizophrenia and affective disorders. J Clin Psychiatry 1983; 44:42–46

7. Maricle R, Hoffman W, Broom J, Faulkner L, Keepers G. The prevalence and significance of medical illness among chronically mentally ill outpatients. Comm Mental Health J 1987; 23:81–90

8. Sheline Y. High prevalence of physical illness in a geriatric psychiatric inpatient population. Gen Hosp Psychiatry 1990; 12:396–400

9. Koranyi E. Morbidity and rate of undiagnosed physical illnesses in a psychiatric clinic population. Arch Gen Psychiatry 1979; 36:414–419

10. Ereole A, Skolol A, Struening E, Curtis J, Millman J. Diagnosis of physical illness in psychiatric patients using DSM-III and a standardized medical history. Hosp Comm Psychiatry 1991; 42:335–400

11. Karasu T, Waltima S, Lindermayer J, Buckley P. The medical care of patients with psychiatric illness. Hosp Comm Psychiatry 1980; 31:463–472

12. Barry KL, Fleming MF, Greenley JR, Kropp S, Widlak P. Characteristics of persons with severe mental illness and substance abuse in rural areas. Psychiatr Serv 1996; 47:88–90

13. Drake RE, Osher FL, Wallace MA. Alcohol use and abuse in schizophrenics: a prospective community study. J Nerv Ment Dis 1989; 177:408–414

14. Dickey B, Azeni H. Persons with dual diagnoses of substance abuse and major mental illness: their excess costs of psychiatric care. Am J Public Health 1996; 86:973–977

15. Hayward RA, Bernard AM, Freeman HE, Corey CR. Regular source of ambulatory care and access to health services. Am J Public Health 1991; 81:434–438

16. Goldberg RJ. Psychiatry and the practice of medicine. South Med J 1995; 88:260–267

17. Shapiro S, Skinner EA, Kessler LG, Von Korff M, German PS, Tischler GL et al. Utilization of health and mental health services: three Epidemiologic Catchment Area sites. Arch Gen Psychiatry 1984; 41:971–978

18. Orleans CT, George LK, Houpt JL, Brodie HK. How primary care physicians treat psychiatric disorders: a national survey of family practitioners. Am J Psychiatry 1985; 142:52–57

19. Hebbs JR, Benner L, Klugman L, Spencer R, Macchia I, Mellinger A, Fife DK. Mortality in a cohort of homeless adults in Philadelphia. N Engl J Med 1994; 331:304–309

20. Wiener JM. Presidential address: Encompassing diversity and demanding equity. Am J Psychiatry 1995; 152:1244–1251

21. Shore JH. Psychiatry at a crossroad: Our role in primary care. Am J Psychiatry 1996; 153:1398–1403

22. Katon W, Von Kroff M, Lin M. Collaborative management to achieve treatment guidelines: impact on depression in primary care. JAMA 1995; 273:1026–1031

23. Crews C, Elasy T, Casper E, Mehler PS. Primary care for the chronically mentally ill. J Gen Intern Med 1996; 11:441–442

24. Shea S, Misra D, Ehrlich MH, Field L, Francis CK. Predisposing factors for severe uncontrolled hypertension in an inner-city minority population. N Engl J Med 1992; 327:779–781

25. Breakley WR, Fischer PJ, Kramer M, Nestadt G, Romanoski AJ, Ross A et al. Health and mental health problems of homeless men and women in Baltimore. JAMA 1989; 262:1352–1357

26. Santos AB, Henggeler SW, Burns DJ, Arana GW, Meisler N. Research on field-based services: models for reform in the delivery of mental health care to populations with complex clinical problems. Am J Psychiatry 1995; 152:1111–1123

27. National Advisory Mental Health Council. Health care reform for Americans with severe mental illness. Am J Psychiatry 1993; 150:1447–1465

28. Young GP, Wagner MB, Kellerman AC, Elgs J, Donley D. Ambulatory visits to hospital emergency departments. JAMA 1996; 276:460–465

29. The Medicaid Access Study Group. Access of Medicaid recipients to outpatient care. N Engl J Med 1994; 330:1426–1430

30. Rask KJ, Williams MV, Parker RM, McNagny SE. Obstacles predicting lack of a regular provider and delays in seeking care for patients at an urban public hospital. JAMA 1994; 271:1931–1933

31. Grumbach K, Keane D, Bindman AB. Primary care and public emergency department overcrowding. Am J Public Health 1993; 83:372–378

32. Birnbaum A, Gallagher J, Utkewicz M, Gennis P, Carter W. Failure to validate a predictive model for refusal of care to emergency-department patients. Acad Emerg Med 1994; 1:213–217

33. Hahn SR, Kroenke K, Spitzer RL, Brody D, Williams JBW, Linzer M, Degary FV. Primary care and mental illness. J Gen Intern Med 1996;11:441–442

34. Williams RM. The costs of visits to emergency departments. N Engl J Med 1996; 334:642–646

35. Wasson JH, Sauvigne AE, Mgielnicki RP, Frey WG, Sox CH, Gaudette C. Continuity of outpatient medical care in elderly men: A randomized trial. JAMA 1984; 253:2413–2417

36. Bindman AB, Grumback K, Osmond D, Uranizan K, Stewart AL. Primary care and receipt of preventive services. J Gen Intern Med 1996; 11:269–276

37. Farmer S. Medical problems of chronic patients in a community support program. Hosp Comm Psychiatry 1987; 38:745–749

38. Felker B, Yazel JJ, Short D. Mortality and medical comorbidity among psychiatric patients. Psychiatr Serv 1996; 47:1356–1363

39. Grob GN. Mad, homeless and unwanted. Psych Clin N Am 1994; 17:541–558

40. Rosenheck R, Lam JA: Homeless mentally ill clients' and providers' perceptions of service needs and clients' use of services. Psychiatr Serv 1997; 48:381–386

41. Mechanic D, Aiken LH. Improving the care of patients with chronic mental illness. N Engl J Med 1987; 317:1634–1638

42. Lazarus A. The role of primary care physicians in managed mental health care. Psychiatr Serv 1995; 46:343–345

43. Einstadter D, Cebul RD, Franta PR. Effect of a nurse case manager on post-discharge follow-up. J Gen Intern Med 1996; 4:684–688

44. Lamberg L. Psychiatry and primary care forge new bonds. JAMA 1988; 260:1743–1748

Commentary

A Cry From Within

KIRSTI A. DYER, MD, MS, *Lafayette, California*

Author's Note: I read Dalton Trumbo's 1939 antiwar novel, Johnny Got His Gun, *as a teenager. The plot remained buried in my memory until I started working with comatose, nonresponsive, postoperative or intensive care unit (ICU) patients as a medical student and later as a resident. After one particularly difficult case, the memory of "Johnny"—blind, deaf, dumb, a multiple amputee, sustained in a hospital bed, struggling to communicate with the outside world—began returning to me. The parallels with ICU patients—intubated, lined (with central line, oxygen, feeding tubes), paralyzed—became apparent to me.*

This story raises disturbing questions for which there are no easy answers. How much do ICU patients feel? How do we, as physicians, feel about dealing with these patients? How do we deal with families who want everything, and "everything" may not be in the patient's best interest? How do we interact with these patients who are unable to interact with us?

As the fog starts to clear from my head, I struggle to regain my bearings and begin to explore my surroundings.

What was my last conscious thought before this moment? I remember driving, bright lights coming toward me, swerving to miss the oncoming car, the gruesome sounds of glass breaking, of metal crunching, and of someone nearby screaming; then suddenly stopping. Voices shout, "We have one here! This one is alive!" Rough hands place something around my neck to keep me from moving, shift me to a board, and pull me out of the car. I remember excruciating pain enveloping my body and escalating in intensity until I can stand no more. Thankfully, the blackness of unconsciousness came.

I swim back against the darkness and confusion in my mind and try to open my eyes. I am unable to make my muscles move. I try to speak and realize that a tube blocks my throat. I do not breathe on my own: a machine forces me. I sense another tube in my nose. Efforts to move my arms and legs are useless. My body feels like dead weight. I am paralyzed and may be tied down. I can feel the air passing over my skin, sometimes cool, other times warm. Taking a mental inventory, I discover something in my bladder so I cannot urinate on my own and something else sticking into the right side of my chest, causing me anguish with every mechanical breath. I cannot move my neck; something keeps me from turning. My legs ache constantly, from immobility, with shooting pains and sweat, as a device intermittently squeezes them. What sort of macabre torture chamber have I entered? Please, someone, tell me I am dreaming!

I sense a person in the room, examining me. My eyes are opened, a light shines in, and I vaguely register hazy, blurry objects.

"Pupils still reactive. The patient is still heavily sedated. No apparent seizure activity."

I feel pressure on my outer chest. A stethoscope? My breaths are automatic, not under my own control.

"Lungs clear."

The pressure is over my heart. Is anyone listening? Perhaps I can make my heart beat faster so someone knows that I am alive and I can feel. No one notices. The pressure shifts to my abdomen.

"Bowel sounds are present. We can increase the tube feeds."

I feel hands examine my feet.

"Peripheral pulses strong and intact. Pneumatics in place."

These hands are cold, rough, mechanical, detached. There are also other hands—warm, soft, compassionate, attentive. They turn me gently from side to side to bathe me, reposition my arms and legs, soothe my tired muscles, and ease the pain in my back created by being still for so long. I look forward to these times, with new, freshly powdered sheets. I smell clean. My hand is held lovingly by these comforting, empathic hands. I feel the compassion and warmth conveyed in this simple act of kindness. For just a brief moment, I experience calm and tranquillity. I am at peace in this daymare. I want to believe the voice that tells me I am doing fine and that everything will be all right. But I have my doubts.

They talk about me at my bedside, oblivious to the fact that I can hear all they discuss:

"This is a 34-year-old victim of a motor-vehicle accident who sustained multiple traumatic injuries, including a closed-head injury, a right hemothorax, and bilateral femur fractures. The patient required emergent intubation

(Dyer KA. A cry from within. West J Med 1998; 169:251–252)

From Journey of Hearts: A Healing Place in Cyberspace.™ http://www.journeyofhearts.org.

Reprint requests to Kirsti A. Dyer, MD, MS, 964 Risa Rd, #32, Lafayette, CA 94549. E-mail: email@kirstimd.com.

in the field to maintain an airway. Seizure activity was observed both in the field and on arrival to the emergency department. The patient was paralyzed and sedated to control the seizures. Vasopressors were used on admission to maintain hemodynamic stability and improve cerebral profusion; however, the patient is presumed to have suffered from anoxic brain injury. The EEG [electroencephalogram] shows some baseline activity, but there are no signs of response to painful stimuli."

They talk about me, discuss the treatments, debate the options, but do not touch me. Why? What do they fear? What are they afraid of catching—or of feeling?

How do I break through to them? I cannot move my face or body. I am unable to speak, yet I can feel. I notice every tube, every needle stick and blood draw, every rough hand and gentle caress. I want to scream out, "I *do* hear you! My brain is working! I am alive!" but remain paralyzed and mute.

Time passes. With each new procedure or repositioning, I am abruptly transported back to this daymare. I spend the hours drifting in and out of this altered state. In one daydream, I am running free, my arms and legs carrying me, effortlessly, by a bubbling stream and through sweet-smelling fields of flowers. The air is filled with the joyful songs of birds, and colorful butterflies are playing on the breeze. I am breathing deeply, my heart rate slowing and relaxing in this peaceful, tranquil land. The sun shine downs on me, sharing its warmth and light, until my only conscious thoughts are of peace, contentment, and joy.

In an instant, this world is shattered. Out of clear blue skies comes a bolt of lightning, striking me in the heart. Abruptly I am transported back into the world of cold steel, sterility, and mechanical devices. People, with their faces distorted from concern and panic, are frantically working over me to bring me back and "save me." Why?

I pray for rest and for peace. I hope that every time I escape from this new consciousness to my happier memories, I will not return. Yet, each day I emerge from my dreams to endure the ventilator, the tubes, and the pain. The medications they give me do not suppress my suffering while I am awake. Because I cannot respond and do not flinch during painful procedures, they do not give me anesthetics. I must endure the anguish of needle sticks for blood and tubes replaced in different body openings. I remain in tormented silence.

They start talking about pneumonia, worry about my "vital signs," and debate the treatment options. They mention a "drug-resistant strain" and possible "sepsis." I hear thick mucus being suctioned from my damaged lungs, as the machine is readjusted daily to help me breathe. I am unable to cough or do anything to clear the mucus. I rely on someone else to suction me. I fear I am drowning in my own fluids.

The conversation around me takes on a more dismal, somber tone.

"This is a very sad case. She's been here for over two months now, and we haven't made any progress. It now looks like an ARDS [adult respiratory distress syndrome] picture with a drug-resistant pneumonia. We are concerned about the possibility of sepsis. We don't know if the antibiotics will be effective. She is young and was healthy before the accident. We are working with a strong heart, lungs, and good kidneys; no signs of multisystem organ failure yet. We believe there was brain damage from the head injury, seizures, and presumed anoxic brain injury. The EEG showed some limited brain-wave activity. The family still wants us to be aggressive. We may need to use the ethics committee to help sort out the options. For now, we are continuing with the full-court press. She is a 'full code.'"

Why must they continue to torture me? How much longer do I endure? Don't they realize I am alive, that I can feel? What purpose does this continued anguish serve? I pray that I will find the ability to communicate so I can ask for my suffering to end. Please let me escape, let me depart to my dream state, my fields of warm sunshine. If this is all my life is to be, why can't they just let me go?

Please.

Editorial

A Great Opportunity

JOHN GARDNER HAS said, "Life is full of great opportunities brilliantly disguised as insoluble problems." I write about not only a great opportunity, but a Blue and Gold, Cardinal, British, and Western opportunity. On September 9, 1998, UCSF Stanford Health Care and The British Medical Journal Publishing Group (BMJ Group) purchased the WESTERN JOURNAL OF MEDICINE from Carden Jennings Publishing, Co. Ltd, the company that had purchased the journal from the California Medical Association in September 1996. This is an unprecedented move that will build on the strengths of the journal and its new owners. It shows perseverance, vision, and courage. It demonstrates collaboration between an internationally renowned medical publisher experienced in complex joint ventures and a new academic entity that promises the best of medical research, education, and care.

What are the risks? The great risk is to do nothing during these dangerous times for our profession. The BMJ/UCSF Stanford Health Care partnership has a tough-minded optimism coupled with informed, practical, values-based action. The risks are low.

What are the benefits? Clinicians will find that the journal will be essential to read. It will have expanded resources, more diversity, increasing excellence; readers will find outstanding papers from a wide variety of sources. Authors will have access to a journal with the possibility of international ripples in print and websites as they prepare papers on basic science with clinical implications, clinically-oriented research, reviews, informatics, advances, policy, ethics, economics, patient-centered care, and evidence based medicine. The BMJ will have access to readers and to dynamic talent and material. UCSF Stanford Health Care will be able to affirm its commitment to service and to support the practice of medicine on the front lines.

The future? The journal will be compelling and will capture the attention of readers and the commitment of authors. It will contribute to improving the care of patients. The journal will be a visible, valuable link between clinicians, academic centers and other sources of information and service, policy makers, and patients. It will be of interest to the California Medical Association, which continues to provide services to the journal during this transition. Finally, it will be independent, as it always has been, devoted to publishing the best material from authors from the West, around the country, and around the world.

The story of the journey to this bright future may be told another time. The challenges have been surmountable because of the importance of the goal — to maintain a vibrant voice for medicine. There has been good company along the way. As for now, thank you for your continued support; give us your ideas; watch for big changes next spring. Be with us as we seize this great opportunity.

LINDA HAWES CLEVER, MD
Editor

Correspondence

To the Editor: Stage of disease is the most important prognostic factor in patients with gastric cancer, and it is rare to cure a patient with symptomatic gastric cancer.[2] Early gastric cancer, on the other hand, is effectively treated by gastrectomy with excellent long-term results. Detecting tumors at an earlier stage through some form of screening has, therefore, the largest potential for improving gastric cancer outcome.

Fecal occult blood testing and sigmoidoscopy are recommended as routine screening tests in patients over the age of 50 in the United States to detect colorectal polyps and malignancy. The incidence of gastric cancer (22,800 cases in 1996) in the United States, however, is only one-sixth that of colorectal cancer (133,500 cases in 1996).[2] The lower incidence of gastric cancer makes the yield of screening endoscopy lower than that for colorectal cancer. Also, upper endoscopy is less convenient for patients and more costly than sigmoidoscopy. As a result, screening endoscopy, although a highly sensitive and specific test for gastric cancer, is not considered cost-effective.[3]

A screening program is most likely to be cost-effective in a population with a high incidence of gastric cancer. We calculated the age-adjusted incidence rates of gastric cancer in patients of different ethnicities in Orange and San Diego/Imperial Counties, California to identify whether a population existed that would be suitable for a prospective trial of gastric cancer screening.

Asians in Orange County were at highest risk of developing gastric cancer. The annual age-adjusted risk of gastric cancer in Asian men in Orange County was 3.3 and 3.5 times as high as that in white men from 1988-1990 and 1991-1993, respectively. The annual age-adjusted risk of gastric cancer in Asian women in Orange County was 3.3 and 3.8 times as high as that in white women from 1988-1990 and 1991-1993, respectively. Black men in San Diego/Imperial Counties were approximately twice as likely to develop gastric cancer in comparison to white men. Latino men and women in both Orange and San Diego/Imperial Counties were nearly twice as likely to develop gastric cancer in comparison to white men and women.

The annual age-adjusted incidence of gastric cancer in Asian men in Orange County (31.4/100,000 from 1988-1990 and 26.9/100,000 from 1991-1993) was only slightly lower than the annual age-adjusted incidence of colorectal cancer in this population (38.3/100,000 from 1988-1990 and 38.5/100,000 from 1991-1993). In comparison, the annual age-adjusted incidence of gastric cancer in white men in Orange County (9.4/100,000 from 1988-1990 and 7.7/100,000 from 1991-1993) was much lower than the annual age-adjusted incidence of colorectal cancer in this population (59.1/100,000 from 1988-1990 and 52.1/100,000 from 1991-1993).

The incidence of gastric cancer in patients of Asian descent born in their native countries is even higher than that of Asians born in the United States. For example, the age-adjusted incidence of gastric cancer in men in Japan in five prefectures in the 1980s ranged from 73.6/100,000 to 93.3/100,000.[4] We were unable to stratify gastric cancer incidence based on country of birth but suspect that the incidence of gastric cancer in those Asian men living in Orange County who were born in their native countries is greater than 31.4/100,000. Public policy discussion should address whether the incidence of gastric cancer in this group is high enough to justify the implementation of a gastric cancer screening program. Further discussion is needed to determine which individual or combination of screening tests may be cost-effective in screening for gastric cancer in high-risk populations in this country.

H. pylori is an established risk factor for gastric cancer and between 40% to 60% of cancers of the antrum and body of the stomach have been attributed to infection with this organism.[5,6] While there is no data that *H. pylori* eradication modifies an individual's cancer risk, it is estimated that if 30% of distal cancers could be prevented by screening and treating *H.pylori* infected individuals, $25,000 would be spent per year of life saved.[3] In a high-risk group such as Japanese-Americans, screening and treatment is estimated to require less than $50,000 per year of life saved, even at 5% treatment efficacy. The cost-effectiveness of this primary prevention strategy requires a prospective study to prove its efficacy. Our data indicate that the high incidence of gastric cancer in Asians in Orange County make them a target group in which to implement a trial to assess the cost-effectiveness of identifying and treating H. *pylori* infection to prevent the subsequent development of gastric cancer.

Charles P. Theuer, MD
Department of Surgery
University of California
Irvine Medical Center, Orange, CA, 92868

Hoda Anton-Culver, PhD
Division of Epidemiology
Department of Medicine
University of California
Irvine, Irvine, CA 92612

REFERENCES

1. Wanebo HJ, Kennedy BJ, Chmeil J, et al. Cancer of the stomach: A patient care study by the American College of Surgeons. Ann Surg 1993; 218:583-592

2. Parker SL, Tong T, Bolden S, Wingo PA. Cancer Statistics, 1996. CA-A Cancer Journal for Clinicians. 46(1): 5-27

3. Parsonnet J, Harris RA, Hack HM, Owens DK. Modelling cost-effectiveness of Helicobacter pylori screening to prevent gastric cancer: a mandate for clinical trials. The Lancet 1996; 348: 150-154

4. Parkin DM, Muir CS, Whelan SL, Gao Y-T, Ferlay J and Powell J (Eds). Cancer Incidence in Five Continents, Volume VI. IARC Scientific Publications No. 120, International Agency for Research on Cancer, Lyon, 1992

5. Parsonnet J, Friedman GD, Vandersteen DP, et al. Helicobacter pylori infection and the risk of carcinoma. N Eng J Med 1991; 325:1127-1131

6. Nomura A, Stemmermann GN, Chyou P-H, et al. Helicobacter pylori infection and gastric carcinoma among Japanese Americans in Hawaii. N Eng J Med 1991; 325:1132-1136

Classified Advertisements

The rate for each insertion is **$1.50 per word, with a 30 word ($45) minimum.** Confidential box number charge: $10 each month.
A word is defined as one or more letters bounded by spaces. The following gives some examples:

Linda H. Clever, MD	= 4 words	allergy/immunology	= 1 word
Send CV	= 2 words	Sacramento, CA 95817	= 3 words
A	= 1 word	804-979-8034	= 1 word
February 22, 1997	= 3 words		

Classified display rate $70 per inch. Maximum sizes: 1 column by 5" or 2 columns by 2" (2-1/8" per column). Larger classified ad space by special arrangements.
Copy for classified advertisements should be received not later than **first of the month preceding issue. All copy must be typed or printed.** Classified advertisers using Box Numbers forbid the disclosure of their identity; your inquiries in writing will be forwarded to Box Number advertisers. Although *The Western Journal of Medicine* believes the classified advertisements in these columns to be from reputable sources, we do not investigate the offers made and assume no liability concerning them. The right is reserved to reject, withdraw, or modify all classified advertising copy in conformity with the decisions of the Advertising Committee.

Please Type or Print Advertising Copy

Classified Advertisements Are Payable in Advance
CLASSIFIED ADVERTISEMENTS, THE WESTERN JOURNAL OF MEDICINE
2 WEST TAUNTON AVENUE, BERLIN, NJ 08009
(609) 768-9360; FAX (609) 753-0064
Ads may be placed online at www.wjmed.com

FAMILY PRACTICE

OREGON/SOUTHWEST WASHINGTON

Northwest Permanente, P.C., a stable, physician-managed multispecialty group of over 550 physicians providing quality care to 430,000 members of Kaiser Permanente in Oregon and Southwest Washington, has excellent opportunities for board certified or eligible family physicians. Our medical offices in Portland, Oregon have an outpatient clinical position that includes some urgent care; and our group in Longview has one position that requires OB skills.

Our program offers a professionally stimulating practice in one of the most successful managed care systems in the country. We also offer a competitive salary (signing bonus for Longview), and a full benefits package including a generous retirement program, professional liability coverage, sabbatical leave and more. To receive additional information, please forward inquiry and CV to: W.J. Clark, Director of Professional Resources, Northwest Permanente, P.C., 500 NE Multnomah, Suite 100, Portland, OR 97232-2099. (800) 813-3763. EOE.

KAISER PERMANENTE
Northwest Permanente, P.C.
Physicians and Surgeons

IDAHO

Make One Of America's Best Places to Live Even Better.

Where You'll Work.
Primary Health, Idaho's largest, fastest-growing integrated health care system whose network of family medicine immediate care centers, by-appointment family practitioners, pediatricians and OB/GYNs serves beautiful southern Idaho.

Where You'll Live.
In a great place to raise a family with quality schools, incredible outdoor recreation and a rural atmosphere close to a metropolitan area with a beautiful performing arts center, excellent hospitals and professional sports.

What You'll Get.
The financial backing and medical resources of a major health care network. A competitive salary, ownership options, flexible work and call schedules, professional growth, full benefits including medical and dental and much more

Submit CV and questions to:
BECKY NELSON
(800) 688-5008 ext. 507 • FAX (208) 344-4262
Physician Recruitment
800 Park Boulevard, Suite 760
Boise, Idaho 83712

CALIFORNIA

LOCUM TENENS
PERMANENT PLACEMENTS

Jim Ellis (800) 437-7676

PHYSICIANS WANTED

OREGON AND THE NORTHWEST. Urban, suburban, rural locations; variety of practice arrangements; all specialties. Placement professionals for 20 yrs. Oberto & Associates, 920 Pinecrest Terr, Ashland, OR 97520. (800) 482-6656; FAX (541) 482-4951. No J-1 Opp. boberto@jeffnet.org.

IMMEDIATE OPENING FOR ORTHOPEDIC SURGEON in South Central Michigan Area. Excellent Opportunity; Fine Community; Excellent Lakes and Golf Courses; 4-Seasons Weather; Excellent Schools; 30 minutes from University of Michigan and Michigan State University. Fax CV to (517) 784-1189 or write to Nicholas W. Bartz, DO, Medical Director, PO Box 885, Jackson, Michigan 49204.

INTERNIST BC/BE or Rheumatologist with interest in primary care to join three person practice north of San Francisco. Send CV to C. Clark-Sayles, MD, 311 Miller Avenue, Suite B, Mill Valley, CA 94941.

CALIFORNIA, NORTHERN - Internist needed for 80+ physician group affiliated with Catholic Healthcare West. Hospital and office based practice (50-50) with shared call, competitive income and benefits. Contact: Danise Cooper, 1-800-765-3055, ID#: 6118WE, Fax: 314-726-3009. Visit our website at www.cejka.com

FAMILY PRACTICE - MILWAUKEE, WISCONSIN LAKESIDE: Join two board certified family physicians in a unique practice opportunity-integrated health care for women and their families with a health plan focused on wellness through holistic, preventative programs including yoga, acupuncture, massage, stress management, etc. OB is optional, excellent and flexible call arrangement, teaching opportunities also available. Brand new beautiful clinic with a unique design, comprehensive benefit package. Call Laurie Myers, 800-338-7107 or fax CV 414-427-7251 or e-mail: fha@execpc.com

HOSPITALIST/PULMONOLOGIST - NORTHERN CALIFORNIA - Excellent opportunity for BC/BE HOSPITALIST/PULMONOLOGIST to join an 80+ physician multispecialty medical group in beautiful Santa Cruz, California, located on Monterey Bay, 90 miles south of San Francisco. If you are interested, please send current CV and three references with phone numbers to: President/CEO, Santa Cruz Medical Clinic, 2025 Soquel Avenue, Santa Cruz, CA 95062

OCCUPATIONAL MEDICINE Locum Tenens Pacific Northwest - Northwest Permanente, P.C., a physician-managed, multispecialty group, has a full-time, six-month to one-year locum tenens opportunity available for a Board Certified and/or residency trained occupational medicine physician or other relevant primary care trained physician, at our medical offices in Oregon and Southwest Washington. Our Occupational Health Program has 19 physicians and covers outpatient clinics at nine sites with 65,000 visits per year, an Employee Health Service, and an Environmental Safety Program serving nearly 6,000 employees. We offer a competitive salary and benefit package which includes family medical insurance, paid time off, professional liability coverage, and a relocation allowance. Please forward C.V. to: W.J. Clark, Director of Professional Resources, NORTHWEST PERMANENTE, P.C., 500 NE Multnomah St., Suite 100, Portland, OR 97232-2099. (800) 813-3763. EOE.

PHYSICIANS WANTED

INTERNAL MEDICINE - NORTHERN CALIFORNIA - Excellent opportunity for BC/BE General Internist to join an 80+ physician multispecialty medical group in beautiful Santa Cruz, California, located on Monterey Bay, 90 miles south of San Francisco. If you are interested, please send current CV and three references with phone numbers to: President/CEO, Santa Cruz Medical Clinic, 2025 Soquel Avenue, Santa Cruz, CA 95062

Since 1979
the

LOCUM TENENS NETWORK has been taking the hassles of the paperwork and overhead out of practicing medicine. Practice near home or travel the country. We will coordinate all your travel details and provide you with the best occurrence malpractice policy available. Explore a partnership with Interim Physicians and open new horizons for your future.

Call today! (800) 333-7828

WESTERN STATES OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 100 positions of various specialties. Both permanent and locum tenens. Send CV to:

Western States Physician Services
7510 No. Trellis Circle, Fresno, CA 93720
Call (800) 873-0786; FAX (800) 705-7943
email: weserve@lightspeed.net

The Western Journal of Medicine

Reprints

Any article printed in *WJM* can be purchased in quantities of 100 or more. Printed on fine quality journal stock. Prices are based upon article length and quantity ordered.

Call Allison Spearman for prices and information, 8:30 – 5:30 EST, Mon– Fri, (804) 979-8034 ext. 146; or E-Mail to: aspearman@cjp.com

ADVERTISING INDEX

Southern Medical Association . . . . . .2nd Cover
MEDICINE + PSYCHIATRY . . . . . .3rd Cover
THE QUEST FOR MERCY . . . . . .4th Cover

Statement of ownership, management, and circulation required by 39 U.S.C. 3685.
WESTERN JOURNAL OF MEDICINE

Publication no.: 084-480. Published monthly by Carden Jennings Publishing Company, Ltd., 1224 W. Main Street, Charlottesville, VA 22903. Number of issues published annually: 12. Editor: Linda Hawes Clever, MD, Western Journal of Medicine, 221 Main Street, San Francisco, CA 94104. Managing Editor: Allison Spearman, Carden Jennings Publishing, 1224 W. Main Street, Charlottesville, VA 22903. Owned by the British Medical Journal Publishing Group, BMA House, Tavistock Square, London WC1H 9JP, England.
Known bondholders, mortgagees, and other security holders owning or holding 1 percent or more of total amount of bonds, mortgages, or other securities: none.
Extent and nature of circulation: Average no. of copies each issue during preceding 12 months: 6704; single issue nearest to filing date: 6482. Paid and/or requested circulation (1) sales through dealers and carriers, street vendors, and counter sales (not mailed): average no. copies each issue during preceding 12 months: 0; single issue nearest to filing date: 0 (2) paid or requested mail subscriptions: average no. copies each issue during preceding 12 months: 6148; single issue nearest to filing date: 5983. Free distribution by mail: average no. copies each issue during preceding 12 months: 240; single issue nearest to filing date: 239. Free distribution outside the mail: 160; single issue nearest to filing date: 160. Total distribution: average no. copies each issue during preceding 12 months: 6548; single issue nearest to filing date: 6382. Copies not distributed: average no. copies each issue during preceding 12 months: 156; single issue nearest to filing date: 100. Percent paid and/or requested circulation: average no. copies each issue during preceding 12 months: 94%; single issue nearest to filing date: 94%.

William T. Carden, Jr., Publisher

Charter Subscription Rate!

Medicine
Psychiatry™
The Official Journal of the
Association of Medicine and Psychiatry

PHYSICIANS INTEGRATING
MEDICAL AND PSYCHIATRIC
KNOWLEDGE

- Original articles, reviews and case reports
- Clinical case conferences from Massachusetts General Hospital
- Content originating from the psychiatric problems that present in the primary care setting, emergency room, medical/psychiatric unit, geriatric unit, and consultation service

Charge my: ❑ Visa ❑ MasterCard ❑ Check enclosed ❑ Bill me

Card # _____

Exp. Date _____

Signature _____

Name _____

Institution/Title _____

Medical Specialty _____

Percentage of professional time spent: ___%Clinical ___%Research

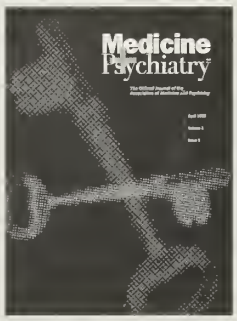
___%Teaching ___%Admin. ___%Other _____

Address _____

City, State, Zip _____

Phone _____

Fax _____



Check One (4 issues)

- ❑ $100 Individual Charter Rate
- ❑ $200 Institutional Rate
- ❑ $75 In-Training Rate
- ❑ $250 Outside North America

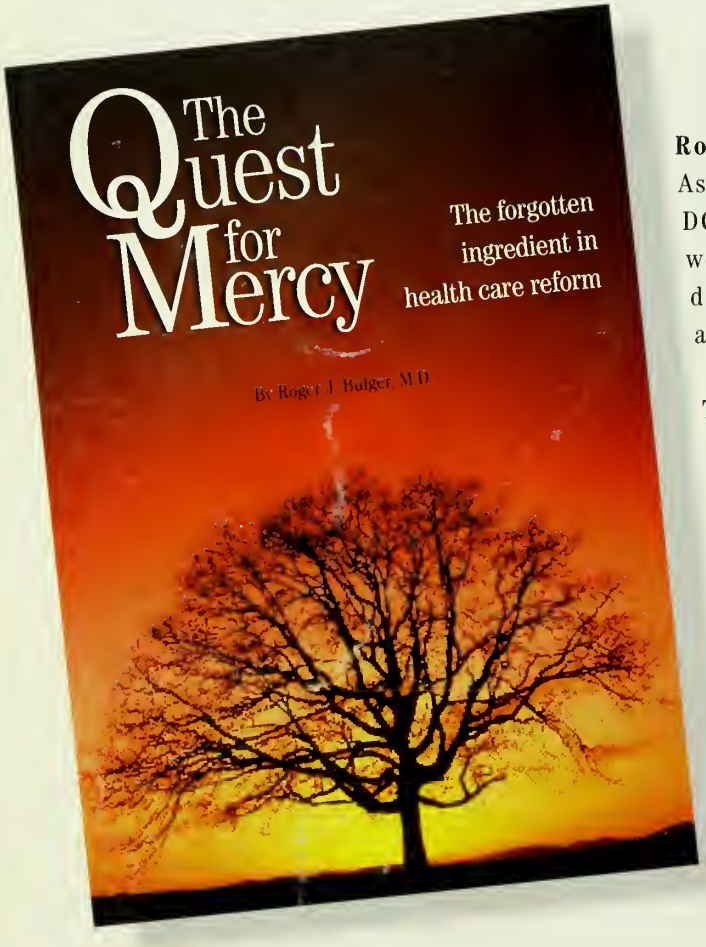
MP98

Return to: Medicine + Psychiatry, 1224 West Main Street, Suite 200
Charlottesville, VA 22903-2858 Phone (804) 979-4913 Fax (804) 979-4025

The Quest for Mercy

The forgotten ingredient in health care reform

by Roger J. Bulger, MD, FACP



Roger J. Bulger, MD, FACP is President of the Association of Academic Health Centers in Washington, DC. He has published scores of papers and chapters, as well as three books on subjects ranging from infectious diseases to medical education, humanities, Hippocrates, and, of course, academic health centers.

The Quest for Mercy is aimed at physicians, including young physicians and medical students. The book addresses managed care and managed cost, sickness and healing, hope and despair, relationships, oaths, populations, prevention, and patients.

"This book will become a classic."

Linda Hawes Clever, MD
Editor, THE WESTERN JOURNAL OF MEDICINE

The Complete Manuscript As Published In
The Western Journal of Medicine

ORDER YOUR COPIES NOW!

Per Copy: $10.00*

*Note: USA/Canada postage and handling included, all other countries please add US $6.00 Air Printed Matter postage. Please add Virginia and local sales tax where applicable. Quantity discounts available; please call.

I would like to order_____copy(ies) of **The Quest For Mercy**.

Payment must accompany order. Total amount enclosed $_____

NAME _____

INSTITUTION _____

ADDRESS _____

CITY/STATE/ZIP _____

COUNTRY _____

❑ Check Enclosed $_____ *please charge my* ❑ VISA ❑ MASTERCARD
(*make payable to:* The Western Journal of Medicine)

Account #_____ Exp. date _____

Signature _____

CARDEN JENNINGS
PUBLISHING CO., LTD

MAIL TO: *The Western Journal of Medicine*, 1224 West Main Street, Suite 200, Charlottesville, Virginia 22903-2858
Phone: (804) 979-8034 • Fax: (804) 979-4025 • www.wjmed.com

OFFICIAL JOURNAL OF

ARIZONA MEDICAL ASSOCIATION · CALIFORNIA MEDICAL ASSOCIATION · DENVER MEDICAL SOCIETY · IDAHO MEDICAL ASSOCIATION · NEVADA STATE MEDICAL ASSOCIATION · NEW MEXICO MEDICAL SOCIETY · UTAH MEDICAL ASSOCIATION · WASHINGTON STATE MEDICAL ASSOCIATION · WYOMING MEDICAL SOCIETY

The Western Journal of Medicine

DISPLAY SHELVES

VOLUME 169 • NUMBER 5 NOVEMBER 1998

ARTICLES

265 Antibiotic Resistance in Bacterial Urinary Tract Infections, 1991 to 1997
IE DYER, TM SANKARY, and JA DAWSON

269 Prevention Services in Primary Care: Taking Time, Setting Priorities
M RAFFERTY

276 Vancomycin-Resistant Enterococcal Colonization in Nonhospitalized HIV-Infected Patients
VK DHAWAN, R NACHUM, N BHAT, L TOLBERT, and M AGRAWAL

280 Dysfunctional Uterine Bleeding
BH CHEN and LC GIUDICE

EPITOMES

285 Important Advances in Radiology

ALERTS, NOTICES, AND CASE REPORTS

293 Illness Associated With Eating Seaweed, Hawaii, 1994
KLE MARSHALL and RL VOGT

295 Sphenoid Pneumoceles Cause Episodic Pressure-Related Blindness
MM HANASONO, AM NORBASH, K SHEPARD, and DJ TERRIS

299 *Salmonella enteriditis* Infections from Shell Eggs: Outbreaks in California
JC MOHLE-BOETANI, SB WERNER, S ABBOTT, N BENDANA, R BRYANT, M FENSTERSHEIB, M GINSBERG, L GRESHAM, J KOEHLER, and L MASCOLA

TOPICS IN PRIMARY CARE MEDICINE

304 Cervical Cancer: Developments in Screening and Evaluation of the Abnormal Pap smear
JME WALSH

MEDICAL INFORMATICS

311 Medicine and the Internet
H AKATSU and J KUFFNER

THE FRANCIS A. COUNTWAY LIBRARY OF MEDICINE BOSTON, MA
NOV 18 1998

COMMENTARY

318 False Names
N RENDLEMAN

CORRESPONDENCE

322 Physician-Hastened Death: Blessing or Curse?
DC STOLINSKY

323 Reply to Dr. Stolinsky
S HEILIG and R BRODY

LESSONS FROM THE PRACTICE

324 A New Perspective on the Gatekeeper Role
JE RUBINSTEIN

OTHER FEATURES

260 Continuing Medical Education Activities
325 Poem
326 Classified Advertising
328 Subscription Information
Detailed Table of Contents: 258, 259

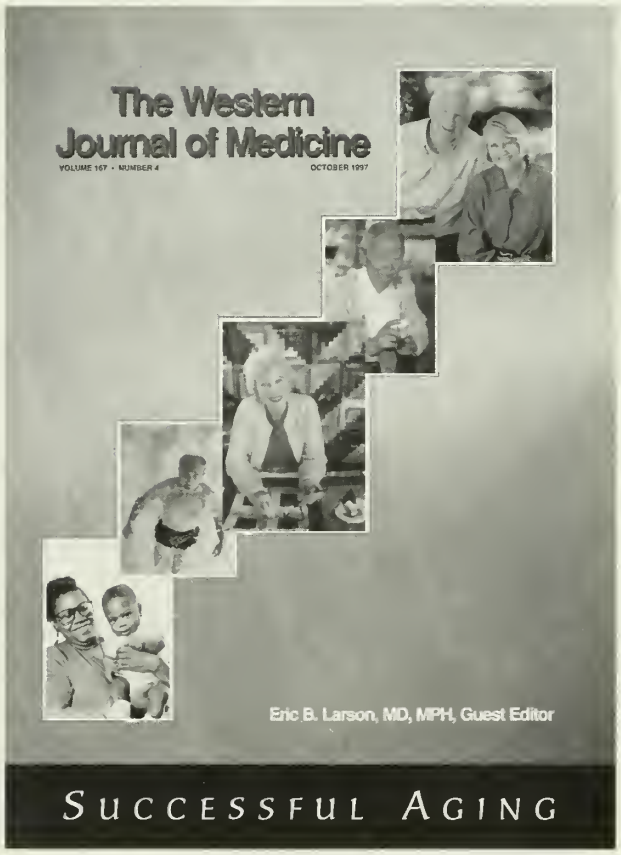
Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Medical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology

A Special Issue of

The Western Journal of Medicine

SUCCESSFUL AGING

Eric B. Larson, MD, MPH, Guest Editor



ARTICLES INCLUDE:

Ways to Make "Usual" and "Successful" Aging Synonymous—Preventive Gerontology
WILLIAM R. HAZZARD, MD

Building Communities That Promote Successful Aging
LINDA P. FRIED, MD, MPH; MARC FREEDMAN, MS; THOMAS E. ENDRES; and BARBARA WASIK, PhD

Healthy Aging—A Woman's Issue
ANDREA Z. LA CROIX, PhD; KATHERINE M. NEWTON, PhD; SUZANNE G. LEVEILLE, PhD; and JEFFREY WALLACE, MD, MPH

Memory, Thinking and Aging—What We Know About What We Know
LINDA TERI, PhD; SUSAN M. MCCURRY, PhD; and REBECCA G. LOGSDON, PhD

Maintaining Good Morale in Old Age
MARK D. SULLIVAN, MD, PhD

Aging and Sexuality
CINDY M. MESTON, PhD

Community Resources for Frail Older Patients
KATHRYN BORGENICHT, MD; ELIZABETH CARTY, MSW; and LAWRENCE Z. FEIGENBAUM, MD

AND MANY MORE!

Order Your Copies Now!

Per Copy: $10.00*

*Note: USA/Canada postage and handling included, all other countries please add US $6.00 Air Printed Matter postage. Please add Virginia and local sales tax where applicable. Quantity discounts available; please call.

I would like to order_____copies of SUCCESSFUL AGING.

Payment must accompany order. Total amount enclosed $ _____

NAME _____

INSTITUTION _____

ADDRESS _____

CITY/STATE/ZIP _____

COUNTRY _____

❑ Check Enclosed $_____ *please charge my* ❑ VISA ❑ MASTERCARD
(*make payable to:* The Western Journal of Medicine)

Account #_____ Exp. date _____

Signature _____

MAIL TO: *The Western Journal of Medicine*, 1224 West Main Street, Suite 200, Charlottesville, Virginia 22903-285
Phone: (804) 979-8034 • Fax: (804) 979-4025 • www.wjmed.com

The Western Journal of Medicine®

SINCE 1902

1224 WEST MAIN STREET, SUITE 200 • CHARLOTTESVILLE, VIRGINIA 22903-2858
TELEPHONE (804) 817-2000; FACSIMILE (804) 817-2020; E.MAIL wjm@cjp.com

LINDA HAWES CLEVER, MD, *Editor*
EDWARD D. HARRIS JR, MD, *Associate Editor*

WALTER G. FINLEY, *Managing Editor*
JANET SHAFER, *Production Monager*
DAVID ERN, *Morketing Director*

editorial communications to DR CLEVER • business communications to MR FINLEY

Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Medical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

SPECIAL EDITORS

Special Editor for Arizona
Marshall B. Block, Phoenix, Ariz

Special Editor for Denver
David Shander, Denver, Colo

Special Editor for Idaho
E. R. W. Fox, Coeur d'Alene, Idaho

Special Editor for Nevada
Anton P. Sohn, Reno, Nev

Special Editor for New Mexico
I. Brian Taylor, Carlsbad, NM

Special Editor for Utah
C. Basil Williams, Salt Lake City, Utah

Special Editor for Washington
David Hopkins, Federal Way, Wash

Special Editor for Wyoming
Joseph P. Murphy, Casper, Wyo

ASSISTANT EDITORS

Clinical Investigation
H. Benfer Kaltreider

Health and Public Policy
Ralph Crawshaw

International Health
Anvar Velji

Lessons From the Practice
Stephen J. McPhee
Jonathan E. Rodnick

Medical Staff Conferences
Nathan M. Bass

Poetry
Margaret Kaufman

Primary Care Medicine
Stephen J. McPhee
Terrie Mendelson

Radiologic Cases
Jonathan M. Levy

EDITORIAL BOARD

Editor Emeritus
Malcolm S. M. Watts, San Francisco, Calif

Anesthesiology
Carol Lake, Sacramento, Calif

Biostatistics and Epidemiology
Virginia L. Ernster, San Francisco, Calif

Cardiac and Thoracic Surgery
Norman E. Shumway, Stanford, Calif

Dermatology
Clifton R. White Jr, Portland, Ore

Emergency Medicine
William A. Boehm, Alamogordo, NM

General and Family Practice
Norman Kahn, Kansas City, Mo
Thomas E. Norris, Seattle, Wash
Joe Schoeber, Casper, Wyo

Internal Medicine
Albert Deisseroth, Houston, Texas
Alan Fogleman, Los Angelas, Calif
Patricia Gabow, Denver, Colo
John H. Holbrook, Salt Lake City, Utah
Philip Hopewell, San Francisco, Calif
Irwin J. Schatz, Honolulu, Hawaii
Walter E. Stamm, Seattle, Wash
Reginald Strickland, Albuquerque, NM
Stephen I. Wasserman, San Diego, Calif

Neurology
Robert Collins, Los Angeles, Calif
John Greenlee, Salt Lake City, Utah
Leslie Wiener, Los Angeles, Calif
Earl Zimmerman, Portland, Ore

Neurosurgery
George A. Ojemann, Seattle, Wash
Robert F. Spetzler, Phoenix, Ariz

Nuclear Medicine
Jerold M. Lowenstein, San Francisco, Calif

Obstetrics and Gynecology
Daniel Mishell Jr, Los Angeles, Calif

Occupational Medicine
Linda Rosenstock, Washington, DC

Ophthalmology
Sandy Feldman, La Jolla, Calif

Orthopedics
Thomas DeCoster, Albuquerque, NM

Pathology
Ronald Weinstein, Tuczon, Ariz

Pediatrics
Allen W. Mathies Jr, Pasadena, Calif
Diane Wara, San Francisco, Calif

Pharmacology
Rubin Bressler, Tucson, Ariz

Physical Medicine and Rehabilitation
Julie G. Madorsky, Pomona, Calif

Preventive Medicine and Public Health
Joseph L. Lyon, Salt Lake City, Utah

Psychiatry
J. Christian Gillin, San Diego, Calif
Lewis Judd, La Jolla, Calif

Radiology
Gary Glazer, Stanford, Calif
Michael L. Manco-Johnson, Denver, Colo
Albert A. Moss, Seattle, Wash

Surgery
Haile T. Debas, San Francisco, Calif
Alex G. Little, Las Vegas, Nev

Urology
Linda Shortliffe, Stanford, Calif

Senior Members at Large
Thomas Elmendorf, Davis, Calif
Edgar Wayburn, San Francisco, Calif

ADVISORY BOARD, CLINICAL INVESTIGATION

Brian A. Cason, San Francisco, Calif
John Christenson, Salt Lake City, Utah
Kari Connolly, San Francisco, Calif
Bruce W. Goldberg, Portland, Ore
Philip Goodman, Reno, Nev
Roy Jones, Albuquerque, NM
Howard Lien, Tucson, Ariz
Barbara M. Lippe, Los Angeles, Calif
Michael W. McDermott, San Francisco, Calif
Jeanette Mladenovic, Denver, Colo
Kenneth M. Moser, San Diego, Calif
James C. Orcutt, Seattle, Wash
John Owings, Sacramento, Calif
Robert Robbins, Stanford, Calif
Henry Rosen, Seattle, Wash
Mary H. Samuels, Portland, Ore
George A. Sarosi, San Jose, Calif
Jeffrey Saver, Los Angeles, Calif
David Schriger, Los Angeles, Calif
Jack H. Simon, Denver, Colo
Peggy Sue Weintrub, San Francisco, Calif
Owen M. Wolkowitz, San Francisco, Calif

DISPLAY & CLASSIFIED ADVERTISING INFORMATION

CONTACT: MJ Mrvica Associates, Inc, 2 West Taunton Ave, Berlin, NJ 08009 • (609) 768-9360/FAX (609) 753-0064
Advertisements—The journal is published the second week of the month. Display advertising must be received no later than the first of the month preceding issue. Advertising rates will be sent on request. Acceptance of advertising is contingent upon approval by the Publisher.
The journal reserves the right to reject any advertisement.

SUBSCRIPTION INFORMATION

The subscription price per year is $65 in the United States and Canada (US funds); $80 in all other countries. Institutional rate $90. Single copies are $10. Special issues are $10. Address all subscription communications to:
THE WESTERN JOURNAL OF MEDICINE Circulation, 1224 W Main St, Suite 200, Charlottesville, VA 22903-2858. • Tel: (804) 817-2000

Allow six weeks for subscriptions to begin. Past issues must be bought individually. So long as reserve stocks are available, missing issue requests from subscribers are honored for up to six months after the issue date. Thereafter, the single copy rate of $10 is applicable for each issue available. Special issues are $10.

Change of Address—Requests for change of address should give both the old and new address. Allow six weeks for changeover.

SUBMITTING MANUSCRIPTS

Manuscripts for consideration should be sent to the managing editor, Walter Finley, 1224 W Main St, Suite 200, Charlottesville, VA 22903-2858.

"Instructions for Authors"—A complete guide to manuscript submission and *WJM* style available from the publisher. Manuscripts may be prepared in accordance with the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals."

PUBLISHER

Copyright © 1998 by the British Medical Journal Publishing Group • Owned and Published by the British Medical Journal Publishing Group

All material subject to this copyright appearing in THE WESTERN JOURNAL OF MEDICINE may be photocopied for the noncommercial purpose of scientific or educational advancement.

Volumes begin with January and July.

THE WESTERN JOURNAL OF MEDICINE (ISSN 0093-0415/USPS 084 480) is published monthly by Carden Jennings Publishing Co, Ltd, 1224 W Main St, Charlottesville, VA 22903-2858. Periodicals postage paid at Easton, Pennsylvania.

POSTMASTER: Send address changes to *The Western Journol of Medicine*, Circulation, 1224 W Main St, Suite 200, Charlottesville, VA 22903-2858.

The Western Journal of Medicine

VOLUME 169 • NUMBER 5 • NOVEMBER 1998

CONTENTS

ARTICLES

265 **Antibiotic Resistance in Bacterial Urinary Tract Infections, 1991 to 1997**

IRENE E. DYER, MS, MPH; TIMOTHY M. SANKARY, MD, MPH; *and* JO ANN DAWSON, MD, MPH

From the Department of Epidemiology, UCLA School of Public Health and the UCLA Student Health Center, Los Angeles, California.

269 **Prevention Services in Primary Care: Taking Time, Setting Priorities**

MICHAEL RAFFERTY, MD

From the Department of Family and Preventive Medicine, Emory University School of Medicine, Atlanta, Georgia.

276 **Vancomycin-Resistant Enterococcal Colonization in Nonhospitalized HIV-Infected Patients**

VINOD K. DHAWAN, MD; RONALD NACHUM, PhD; NIMEC BHAT; LAURIE TOLBERT, RN, BS, PHN; *and* MANJU AGRAWAL, MD

From Charles R. Drew University of Medicine and Science, Martin Luther King Jr.–Charles R. Drew Medical Center, and UCLA School of Medicine, Los Angeles, California.

280 **Dysfunctional Uterine Bleeding**

BERTHA H. CHEN, MD; *and* LINDA C. GIUDICE, MD, PhD

From the Department of Gynecology and Obstetrics/Division of Gynecology, Stanford University, Stanford, California.

EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

Radiology

Items of progress in radiology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, as to both scientific fact and important clinical significance.

285 **Intensity Modulated Radiation Therapy**

CHRISTOPHER M. ROSE, MD, FACR

286 **The Future of Teleradiology in Medicine**

DAVID E. AVRIN, MD, PhD; *and* KATHERINE P. ANDRIOLE, PhD

286 **New Methods of Treatment for Cerebral Aneurysms**

CONSTANTINE C. PHATOUROS, MBBS, FRACR; RANDALL T. HIGASHIDA, MD; *and* VAN V. HALBACH, MD

287 **Extracranial Carotid Stenosis: Ultrasound, MRI, Angiography**

GRETCHEN A. W. GOODING, MD

288 **Ultrasound versus CT in Evaluating Blunt Abdominal Trauma**

JOHN R. RICHARDS, MD

289 **Imaging Renal and Ureteral Stones**

C. DARRYL JONES, MD

290 **Management of Locally Advanced Prostate Cancer: New Definitions and Strategies**

MACK ROACH III, MD

ALERTS, NOTICES, AND CASE REPORTS

293 **Illness Associated With Eating Seaweed, Hawaii, 1994**

KATHERINE L.E. MARSHALL, DVM, MS; *and* RICHARD L. VOGT, MD

From the Epidemic Intelligence Service State Branch, Division of Applied Public Health Training, Centers for Disease Control and Prevention, Atlanta, Georgia, and the Communicable Disease Division, Department of Health, Honolulu, Hawaii.

295 **Sphenoid Pneumoceles Cause Episodic Pressure-Related Blindness**

MATTHEW M. HANASONO, MD; ALEXANDER M. NORBASH, MD; KIMBERLY SHEPARD, MD; *and* DAVID J. TERRIS, MD

From the Division of Otolaryngology/Head and Neck Surgery, and Department of Radiology, Stanford University Medical Center, Stanford, California

299 ***Salmonella enteritidis* Infections from Shell Eggs: Outbreaks in California**

JANET C. MOHLE-BOETANI, MD; SB WERNER, MD, MPH; SHARON ABBOTT; NANCIE BENDANA, PHN; RAYMOND BRYANT; MARTIN FENSTERSHEIB, MD, MPH; MICHELE GINSBERG, MD; LOUISE GRESHAM, PhD, MPH; JANE KOEHLER, DVM; *and* LAURENE MASCOLA, MD

From the Disease Investigation and Surveillance Branch, Division of Communicable Disease Control, California Department of Health Services; Microbial Diseases Laboratory, California Department of Health Services; County of Los Angeles, Department of Health Services; Disease Control and Prevention Unit, Santa Clara County Health and Hospital Systems; County of San Diego, Department of Health Services; and Epidemiology and Prevention Branch, Georgia Department of Human Resources

TOPICS IN PRIMARY CARE MEDICINE

304 **Cervical Cancer: Developments in Screening and Evaluation of the Abnormal Pap Smear**

JUDITH M.E. WALSH, MD, MPH

From the Division of General Internal Medicine, University of California, San Francisco.

MEDICAL INFORMATICS

311 **Medicine and the Internet**

HARUKO AKATSU, MD; *and* JAMES KUFFNER, MS

From the Department of Medicine, Stanford University School of Medicine and the Department of Computer Science, Stanford University School of Engineering, Stanford, California.

COMMENTARY

318 **False Names**

NEAL RENDLEMAN, MD

From the Old Town Clinic, Good Samaritan Hospital Primary Care Internal Medicine Program, Portland, Oregon.

CORRESPONDENCE

322 **Physician-Hastened Death: Blessing or Curse?**

DAVID C. STOLINSKY, MD

323 **Reply to Dr. Stolinsky**

STEVE HEILIG, MPH; *and* ROBERT BRODY, MD

LESSONS FROM THE PRACTICE

324 **A New Perspective on the Gatekeeper Role**

JOAN E. RUBINSTEIN, MD

Dr. Rubinstein is in private practice in Fowler, California.

OTHER FEATURES

260 **Continuing Medical Education Activities**

325 **Poem**

326 **Classified Advertising**

328 **Subscription Information**

THE FRANCIS A. COUNTWAY LIBRARY OF MEDICINE BOSTON, MA

NOV 18 1996

★ Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

Continuing Medical Education

ARIZONA • CALIFORNIA, HAWAII, NEVADA • COLORADO • IDAHO • NEW MEXICO • UTAH • WASHINGTON • WYOMING

ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

CARDIOLOGY

February 7–11, 1999—**International Congress XII on Endovascular Interventions.** Contact: Erika Scott (602) 266-2200 or fax (602) 265-8885. www.endovascularcongress.org

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (520) 626-7832; (800) 328-5868.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Paulette Richardson, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-3387. For more information on accreditation or certification, please write to the above address.

ALLERGY/IMMUNOLOGY

November—**Influenza Pandemic Preparedness.** Center for Disease Control at various sites around state. Thurs. 2.5 hrs. Call California Distance Learning Health Networks for satellite sites and fees (619) 594-3348.

CARDIOLOGY

January 7–10, 1999—**NewEra Cardiac Care: Innovation and Technology.** Marriott's Mountain Shadows Resort, Scottsdale Arizona. Sponsored by the Cardiothoracic Research &Education Forum. Contact:Aligned Management Associates, Inc. P.O. Box 23220, San Diego CA 92193 (760) 751-8841. Fax (760) 751-8842. www.amainc.com

January 18–22, 1999—**The 30th Annual Cardiovascular Conference at Snowmass.** Sponsored by the American College of Cardiology. To be held at Snowmass Conference Center, Snowmass, CO. 23 CME credits. Contact: Registration Secretary, Extramural Programs Dept., American College of Cardiology, 9111 Old Georgetown Rd., Bethesda, MD 20814-1699. Phone (800) 253-4636, ext.695 or Fax (301) 897-9745.

January 29–31, 1999—**Clinical Nuclear Cardiology: Case Review With the Experts. Cardiology Update 1998.** American College of Cardiology at San Francisco. Thurs.–Sat. Contact: ACC Extramural Programs (800) 253-4636.

February 18–20, 1999—**19th Annual Pathophysiology & Techniques of Cardiopulmonary Bypass.** San Diego Marriott Hotel & Marina. Sponsored by the Cardiothoracic Research &Education Forum. Contact:Aligned Management Associates, Inc. P.O. Box 23220, San Diego CA 92193 (619) 541-1444 or fax (619) 541-1447. www.amainc.com

DERMATOLOGY

January 14–17, 1999—**Practical Dermatology for the Primary Care Physician, San Diego, CA.** Sponsored by Continuing Medical Education Associates. To be held at the Hyatt Regency, La Jolla, San Diego, CA. Method: AV, L, SB, W. Thurs–Sun. 20 hrs credit: AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

March 4–7, 1999—**Practical Dermatology for the Primary Care Physician, Orlando, FL.** Sponsored by Continuing Medical Education Associates. To be held at the Buena Vista Palace at Walt Disney World Village, Orlando, FL. Method: AV, L, SB, W. Thus–Sun. 20 hrs credit: AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

May 23–26, 1999—**Practical Dermatology for the Primary Care Physician, Las Vegas, NV.** Sponsored by Continuing Medical Education Associates. To be held at the Caesars Palace, Las Vegas, NV. Method: AV, L, SB, W. Sun–Wed. 20 hrs credit: AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

EMERGENCY MEDICINE

November 9–13—**Emergency Symposium III.** UCSD at La Jolla Marriott, San Diego. Mon.–Fri. 32 hrs. Contact: OCME (619) 534-3940.

December 4–5—**Trauma Care – Then and Now.** UCSF at Hotel Nikko, San Francisco. Fri.–Sat.. 12 hrs. $395-$450. Contact: UCSF (415) 476-5808.

December 14–18— **Emergency Symposium II.** UCSD at La Jolla Marriott, San Diego. Mon.–Fri. 32 hrs. Contact: OCME (619) 534-3940.

March 1–2, 1999—**Improving Emergency Department Patient Satisfaction and Reducing Length of Stay.** Las Vegas, Nevada at Harrah's. Contact: CEME, 5330 Primrose Drive, Suite 250, Fair Oaks, CA 95628. (800) 651-2363.

April 12–13, 1999—**High Risk Emergency Medicine.** Las Vegas, Nevada at Harrah's. Contact: CEME, 5330 Primrose Drive, Suite 250, Fair Oaks, CA 95628. (800) 651-2363.

May 6–7, 1999—**Challenges in Pediatric Emergency Medicine.** Las Vegas, Nevada at Harrah's. Contact: CEME, 5330 Primrose Drive, Suite 250, Fair Oaks, CA 95628. (800) 651-2363.

May 13–16, 1999—**Outdoor Emergency Medicine, Scottsdale, AZ.** Sponsored by Continuing Medical Education Associates. To be held at the Marriott Camelback Inn, Scottsdale, AZ. Method: AV, L, SB, W. Thurs–Sun. 20 hrs credit: AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

May 13–16, 1999—**Outdoor Emergency Medicine, Scottsdale, AZ.** Sponsored by Continuing Medical Education Associates. To be held at the Marriott Camelback Inn, Scottsdale, AZ. Method: AV, L, SB, W. Thurs–Sun. 32 hrs credit: AMA, AOA, AAFP. $750. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

May 20–21, 1999—**High Risk Emergency Medicine.** Las Vegas, Nevada at Harrah's. Contact: CEME, 5330 Primrose Drive, Suite 250, Fair Oaks, CA 95628. (800) 651-2363.

June 3–4, 1999—**Improving Emergency Department Patient Satisfaction and Reducing Length of Stay.** Chicago, IL at the Holiday Inn Chicago City Centre. Contact: CEME, 5330 Primrose Drive, Suite 250, Fair Oaks, CA 95628. (800) 651-2363.

ENDOCRINOLOGY

March 5, 1999—**Diabetes Update: 1999.** UC Davis at Doubletree Hotel, Sacramento, CA. Friday. Contact: UCD (916) 734-5390.

March 11–13, 1999—**The Fourth International Conference on Continuous Renal Replacement Therapies.** Hotel del Coronado in San Diego, California. Contact:Shirley Kolkey, Complete Conference Management, 1660 Hotel Circle North, #220, San Diego, CA 92108. (619) 299-6673 or fax (619) 299-6675.

FAMILY PRACTICE/PRIMARY CARE

November 14—**Women's Health Symposium.** UC Davis at UCD Med Ctr. Cancer Center Auditorium, Sacramento. Sat. Contact: UCD (916) 734-5390.

December 3–4—**Controversies in Women's Health.** UCSF at Cathedral Hill Hotel, San Francisco. Thurs.–Fri. 13 hrs. Credit. $370. Contact: UCSF (415) 476-5208.

January 14–17, 1999—**Practical Dermatology for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Regency, SF. Thurs.–Sun. 20 hrs. $575. Contact: Victoria Gonzales, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

January 14–17, 1999—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Regency, SF. Thurs.–Sun. 20 hrs. $575. Contact: Victoria Gonzales, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

February 11–14, 1999—**Office Gynecology and Women's Health for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Islandia, San Diego. Thurs.–Sun. 20 hrs. $575. Contact: Victoria Gonzales, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

February 12–14, 1999—**California Academy of Family Physicians (CAFP) 51 st Annual Scientific Assembly.** San Diego Concourse, San Diego, CA. 40 hrs. Contact: Clark Franklin, CAFP, 114 Sansome Street, Suite 1305, San Francisco, CA 94104-3824. (415) 394-9121 or fax (415) 394-9119.

February 17 –19, 1999—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF at Cathedral Hill Hotel, SF. Wed.–Fri. 16 hrs. $400. Contact:UCSF Program Coordinator, Dept. of Family and Community Medicine (415) 476-5250.

March 27, 1999—**Primary Care Gastroenterology.** UC Davis at Cancer Center Auditorium, Sacramento, CA. Saturday. Contact: UCD (916) 734-5390.

May 14–18, 1999—**Primary Care Essentials, San Francisco, CA.** Sponsored by Continuing Medical Education Associates. To be held at the Grand Hyatt on Union Square, San Francisco, CA. Method: AV, L, SB, W. Thurs–Sun. 32 hrs credit: AMA, AOA, AAFP. $750. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

GERIATRICS

November 8–11—**Geriatrics Update 1998.** Sponsored by Continuing Medical Education Associates. Loews Coronado Bay Resort, San Diego, CA. Sun.–Wed. 20 hrs. Credit: AMA, AOA, AAFP. $525. Contact: Victoria Gonzales, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

INFECTIOUS DISEASE

November 19—**Preparing for the Coming Influenza Pandemic Satellite Course.** California Distance Learning Health Network at various sites throughout California. Thurs. 2.5 hrs. Fee varies. Contact:CDLHN (619) 594-3348.

December 2–6—**Internal Medicine- 1998 Fall Program.** Sponsored by Continuing Medical Education Associates. Boca Raton Resort and Club, Boca Raton, FL. Wed.–Tues. 30 hrs. Credit: AMA, AOA, AAP, AAFP. $750. Contact: Victoria Gonzales, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

December 3—**Surveillance of Vaccine-Preventable Diseases Satellite Course.** California Distance Learning Health Network at various sites throughout California. Thurs. 2.5 hrs. Fee varies. Contact:CDLHN (619) 594-3348.

December 9—**AIDS-Associated Malignancies: Biology and Clinical Management.** UCSF at Palace Hotel, San Francisco. Wed. Credit 4.5 hours. $135. Contact: UCSF (415) 476-5208.

December 10–12—**Clinical Care of the AIDS Pateient.** UCSF at Palace Hotel, San Francisco. Thurs-Sat. Credit 24 hours. $455. Contact: UCSF (415) 476-5208.

February 5–6, 1999—**Infectious Disease Update: 1999.** UC Davis at Hilton Hotel, Sacramento. Fri-Sat. Contact: UCD (916) 734-5390.

February 21–26, 1999—**Winter Course in Infectious Diseases, Snowmass, Colorado-25th Anniversary Meeting.** Sponsored by the Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine and Research Institute, Palo Alto Medical Foundation. 28 hrs. $75–$350. Contact: Trisha Mitchell, Meeting Coordinator (800) 535-7814 or fax (215) 422-1283.

INTERNAL MEDICINE

March 19–25, 1999—**Internal Medicine, San Diego CA.** Sponsored by Continuing Medical Education Associates. To be held at the Hotel del Coronado, San Diego, CA. Method: AV, L, SB, W. Fri–Thurs. 45 hrs credit: AMA, AOA, AAFP. $895. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

NEPHROLOGY

February 4–6, 1999—**Advanced Nephrology: Nephrology for the Consultant.** Sponsored by UC San Diego. To be held at the Coronado Island Marriott Resort, Coronado, CA. 17 hrs credit:AMA. $175, $425. Contact: Shirley Kolkey, 1660 Hotel Circle North, #220, San Diego, CA 92108. Phone (619) 299-6673 or Fax (619) 299-6675; e-mail c-c-m@worldnet.att.net

NEUROLOGY

February 10–12, 1999—**Recent Advances in Neurology.** UCSF at Mark Hopkins Inter-Continental Hotel, San Francisco. Wed–Fri. 15 hrs. $425. Contact: UCSF (415) 476-0318.

OB/GYN

December 6—CTTR **105th Semi-Annual Cancer Seminar: Tumors of the Breast.** To be held at the Marriott at Coronado, San Diego. 8 hrs. $110, $265. Contact: California Tumor Tissue Registry; c/o LLU School of Medicine, 11021 Campus Ave., AH 335, Loma Linda, CA 92350. Phone (909) 824-4788 or Fax (909) 478-4188; email cttr@linkline.com.

February 11–14, 1999—**Office Gynecology and Women's Health for the Primary Care Physician, San Diego, CA.** Sponsored by Continuing Medical Education Associates. To be held at the Hyatt Islandia, San Diego, CA. Method: AV, L, SB, W. Thurs–Sun. 20 hrs credit: AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

February 25–28, 1999—**Office Gynecology and Women's Health for the Primary Care Physician, Orlando, FL.** Sponsored by Continuing Medical Education Associates. To be held at the Buena Vista Palace at Walt Disney World Village, Orlando, FL. Method: AV, L, SB, W. Thurs–Sun. 20 hrs credit: AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

ORTHOPEDICS

January 14–17, 1999—**Office Orthopedics and Bone Radiology for the Primary Care Physician, San Diego, CA.** Sponsored by Continuing Medical Education Associates. To be held at the Hyatt Regency, La Jolla, San Diego, CA. Method: AV, L, SB, W. Thurs–Sun. 20 hrs credit: AMA, AOA, AAFP. $575. Contact: CMEA Monica L. Lier. (800) 993-2632 or (619) 674-5200.

February 25–28, 1999—**Office Orthopedics and Bone Radiology for the Primary Care Physician, New Orleans, LA.** Sponsored by Continuing Medical Education Associates. To be held at the Royal Sonesta Hotel, New Orleans, LA. Method: AV, L, SB, W. Thurs–Sun. 20 hrs credit: AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

February 25–28, 1999—**Office Orthopedics and Bone Radiology for the Primary Care Physician, Las Vegas, NV.** Sponsored by Continuing Medical Education Associates. To be held at the Caesars Palace, Las Vegas, NV. Method: AV, L, SB, W. Sun–Wed. 20 hrs credit: AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

KEY TO ABBREVIATIONS

DREW:	Charles R. Drew Postgraduate Medical School, Office of Continuing Medical Education, (213) 563-4800.
LLU:	Loma Linda University, Continuing Medical Education Programs, (909) 824-4963.
STAN:	Stanford University, Postgraduate Education. (415) 723-5594.
UCD:	University of California, Davis, Office of Continuing Medical Education, (916) 734-5390.
UCI:	University of California, Irvine, Memorial/UCI Center for Health Education, (714) 824-5926.
UCLA:	University of California, Los Angeles, Continuing Education in Medicine and Health Sciences, (310) 794-2620.
UCSD:	University of California, San Diego, Office of Continuing Medical Education, (619) 534-3940.
UCSF:	University of California, San Francisco, Extended Programs in Medical Education, (415) 476-4251.
USC:	University of Southern California, Postgraduate Division, (800) USC-1119.

PATHOLOGY

December 6—**CTTR 106th Semi-Annual Cancer Seminar: Tumors of the Head and Neck.** To be held at the Westin South Coast Plaza, Costa Mesa. 8 hrs. $110, $265. Contact: California Tumor Tissue Registry; c/o LLU School of Medicine, 11021 Campus Ave., AH 335, Loma Linda, CA 92350. Phone (909) 824-4788 or Fax (909) 478-4188; email cttr@linkline.com.

PEDIATRICS

December 4–6—**Stabilization and Management of the Critically Ill Child.** UCSF at Grand Hyatt Hotel, SF. Fri–Sun. 12 hrs. $300. Contact: UCSF (415) 476-5808.

January 29–31,1999—**37TH Clinical Conference Pediatric Anesthesiology.** Disneyland Hotel, 1150 W. Cerritos Avenue, Anaheim, CA 92802. Sponsored by The Pediatric Anesthesiology Foudation. $250-$295. Contact David J Steward, M.B., Program Director, Pediatric Anesthesiology Conference Box #3, Childrens Hospital Los Angeles, P.O. Box 54700, Los Angeles, CA 90054. Phone (213) 669-2262 or Fax (213) 660-8983.

February 14–17, 1999—**Pediatrics Update 1999, San Diego, CA.** Sponsored by Continuing Medical Education Associates. To be held at the Hyatt Islandia, San Diego, CA. Method: AV, L, SB, W. Sun–Wed. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

February 28–March 3, 1999—**Pediatrics Update 1999, Orlando, FL.** Sponsored by Continuing Medical Education Associates. To be held at the Buena Vista Palace at Walt Disney World Village, Orlando, FL. Method: AV, L, SB, W. Sun–Wed. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

March 19–20, 1999—**Pediatrics Update: 1999.** UC Davis at Cancer Center Auditorium, Sacramento, CA. Fri–Sat. Contact: UCD (916) 734-5390.

RADIOLOGY

February 25–28, 1999—**Up to Date Radiology in the Desert.** Mira Monte Resort, Indian Wells, California. Credit 26 hrs. AMA. $495-$750. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

RESPIRATORY

March 19–20, 1999—**Cystic fibrosis Caregivers Symposium.** UC Davis at Marriott Hotel, Napa, CA. Fri–Sat. Contact: UCD (916) 734-5390.

SURGERY

January 15–16, 1999—**What's New General Surgery.** UC Davis at Hyatt Regency Sacramento at Capitol Park. Fri–Sat. Contact: UCD (916) 734-7203.

UROLOGY

December 11–12—**Practical Issues in Human Sexuality and Erectile Dysfunction.** UCSF at Ritz-Carlton Hotel, SF. Fri–Sat. 14.5 hrs. $385. Contact: UCSF (415) 476-5808.

GENERAL/MULTIDISCIPLINARY

January 29–31, 1999—**Research Study Club, 65th Clinical Conference.** To be held at the Universal City Hilton & Towers, CA. 15 hrs credit. $190–$400. Contact: Mrs.Ball (909) 677-4482 or fax (909) 677-7904; email: lbll@aol.com.

April 28–May 8, 1999—**Blue Water Medical Seminar.** Tri City Medical Center at Baja California aboard Royal Star Sportfisher. Wed–Sun. 20 hrs. $3300. Contact: Ronald Mcdak (760) 727-7863.

May 16–19, 1999—**Alternative Medicine, Scottsdale, AZ.** Sponsored by Continuing Medical Education Associates. To be held at the Mariott Camelback Inn, Scottsdale, AZ. Method: AV, L, SB, W. Sun–Wed. 20 hrs credit: AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

June 22–29, 1999—**Mindfulness-Based Stress Reduction in Mind-Body Medicine.** To be held at the Mana Lae Retreat Center, Maui, Ha. $995. Contact: Steve Flowers (530) 898-1495.

LOSS PREVENTION

November 10—**Preventing "Failure to Diagnose" Malpractice Claims.** Medical Insurance Exchange of California. at San Francisco Medical Society. Wed. Free or $40 to nonmembers. Contact: David Carp (800) 227-4527.

November 11—**Medical Records Documentation for Patient Safety and Physician Defensibility.** Medical Insurance Exchange of California. at Embassy Suites Hotel, Walnut Creek. Wed. Free or $40 for nonmembers. Contact: MIE (800) 227-4527.

HOME STUDY/SELF ASSESSMENT

California Physicians' Legal Handbook Series. California Medical Association. Contact: CMA, PO Box 7690, San Francisco 94120-7690. (800) 882-1262.

Breast Cancer, Early Detection and Control. Texas Medical Association. **CD ROM.** $70. 2 hrs. Contact: Texas Medical Association, (800) 880-1300; http://www.texmed.org/health_science/hs_poep.html

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Second Wednesday of Each Month—**Cardiovascular Education Series.** St Anthony Hospital at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

February 4–6, 1999—**Neurology For The Non-Neurologist.** Hyatt Regency, Cancun Mexico. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

February 5–7, 1999—**Arrhythmias: Interptretation, Diagnosis & Management** MGM Grand, Las Vegas, NV Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

February 12–14, 1999—**Clinical Endocrinology For Primary Care Physicans.** Beaver Run Resort, Breckenridge, CO.Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

February 19–21, 1999—**Managing Respiratory Diseases.** Marriot's Casa Marina, Key West, FL. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

February 25–27, 1999—**Dermatology For The Non-Dermatologist.** Atlantis Paradise Resort, Bahamas. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

February 26–28, 1999—**Coronary Heart Disease Update.** Hilton Tapatio Cliffs, Scottsdale, AZ. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

March 12–14, 1999—**Dermatology For The Non-Dermatologist.**Riviera Hotel & Casino, Las Vegas, NV. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

March 25–27, 1999—**Neurology For The Non-Neurologist.** Grand Beach Resort, St. Thomas, USVI. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

March 25–27, 1999—**Clinical Endocrinology For Primary Care Physicans.** Marriott's Beach Resort, St. Grand Cayman. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

March 26–28, 1999—**Managing Respiratory Diseases.** Buena Vista Palace,Orlando,FL. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 8–10, 1999—**Coronary Heart Disease Update.** Hyatt Regency, Aruba Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 8–10, 1999—**Clinical Endocrinology For Primary Care Physicans.** The Westin Resort, St John, USVI. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 9–11, 1999—**Arrhythmias: Interptretation, Diagnosis &Management** Hilton Tapatio Cliffs, Scottsdale, AZ. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 9–11, 1999—**Neurology For The Non-Neurologist.** Marriott's Casa Marina, Key West, FL. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 23–25,1999—**Managing Respiratory Diseases.** Bally's, Las Vegas, NV. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 23–25,1999—**Dermatology For The Non-Dermatologist.** Parc Fifty-five, San Francisco, CA. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 30–May 2, 1999—**Dermatology For The Non-Dermatologist.** South Sea Plantation, Captiva Island, FL. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 30–May 2, **Clinical Endocrinology For Primary Care Physicans.** Hyatt Regency, New Orleans, LA. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

May 14–16, 1999—**Managing Respiratory Diseases.** Hilton Resort, Hilton Head, SC. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

May 14–16, 1999—**Neurology For The Non-Neurologist.** Bally's, Las Vegas, NV. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave. Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

IDAHO

The listing of continuing medical education programs in Idaho is compiled by the Ada County Medical Society. To list CME programs here, please send information at least two months in advance to: Ada County Medical Society, Inc. 305 W. Jefferson, PO Box 2668, Boise, Idaho 83701. (208) 336-2930.

Brochures, course information, and registration forms are available from the contact person or organization.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

Every First and Third Tuesday—**Building and Implementing Clinical Practice Guidelines at the Point of Care.** Contact: Thomas A. Naegele, DO, (505) 275-7267.

SATELLITE COURSES

Contact: Joe Treat or Jim Cato, Immunization Program, (505) 827-2366.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

January 6–10, 1999—**MRI at Snowbird.** Cliff Lodge, Snowbird, Utah. Credit 20 hrs. AMA. $400-$650. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773 or fax (770)552-9859; email: webmaster@ryalsmeet.com. www.ryalsmeet.com

MEDICAL GRAND ROUNDS

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics.** Contact: UUSM.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Ave, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 S Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 340-2058.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Ste 1100, Seattle, WA 98121. (206) 441-9762.

OTHER CME OPPORTUNITIES

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

Annual Meeting and Course: International Spine Imaging Symposium. February 15–17, 1999. Registry Resort, Naples, Florida. Credit 19.5 hrs. AMA. $250–$650. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

Breast Imaging Today and Tomorrow. January 25–28, 1999. Boca Raton Resort and Club, Boca Raton, Florida. Credit 23 hrs. AMA. $495–$695. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

Breast Imaging Today and Tomorrow. February 15–19, 1999. Buena Vista Palace Resort and Spa, Lake Buena Vista, Florida. Credit 23 hrs. AMA. $495–$695. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

Conference on Patient Education. November 11–14, 1998. Hyatt Regency Austin, Austin, Texas. Contact: Ray Rosetta, Meetings and Programs Director, Society of Teachers of Family Medicine, 8880 Ward Parkway, Kansas City, Missouri 64114. Phone (800) 274-2237, ext. 4512.

Conference on Patient Education. November 19–22, 1998. Disney's Coronado Springs Resort, Orlando, Florida. Contact: Ray Rosetta, Meetings and Programs Director, Society of Teachers of Family Medicine, 8880 Ward Parkway, Kansas City, Missouri 64114. Phone (800) 274-2237, ext. 4512.

Musculoskeletal MR. January 18–22, 1999. The Ritz-Carlton Resort Hotel, West Palm Beach, Florida. Credit 22.5 hrs. AMA. $450–$695. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

Predoctoral Education Conference. February 4–7, 1999. Savannah Marriott Riverfront, Savannah, Georgia. Contact: Ray Rosetta, Meetings and Programs Director, Society of Teachers of Family Medicine, 8880 Ward Parkway, Kansas City, Missouri 64114. Phone (800) 274-2237, ext. 4512.

STFM Family Conference. March 3–7, 1999. Kiawah Resort, Kiawah Island, South Carolina. Contact: Ray Rosetta, Meetings and Programs Director, Society of Teachers of Family Medicine, 8880 Ward Parkway, Kansas City, Missouri 64114. Phone (800) 274-2237, ext. 4512.

5th Annual Neuroradiology: A Comprehensive Review. February 2–6, 1999. The Ritz-Carlton Resort Hotel, West Palm Beach, Florida. Credit 24 hrs. AMA. $450–$695. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

32nd Annual Spring Conference. April 28–May 2, 1999. Sheraton Seattle Hotel & Towers, Seattle, Washington. Contact: Ray Rosetta, Meetings and Programs Director, Society of Teachers of Family Medicine, 8880 Ward Parkway, Kansas City, Missouri 64114. Phone (800) 274-2237, ext. 4512.

35th Annual Forensic Dentistry. March 7–11, 1999. Holiday Inn, Silver Spring, Maryland. Credit 38 hrs. $300–$675. Contact: Ruth Murphy, CAME, Armed Forces Institute of Pathology, Washington, DC 20306-6000; (800) 577-3749 or (202) 782-2637; email: came@afip.osd.mil; www.afip.org.

58th Annual American Occupational Health Conference. April 23–30, 1999. Ernest N. Morial Convention Center, New Orleans, Louisiana. Contact: ACOEM Education Dept., 55 W. Seeger Road, Arlington Heights, IL 60005; (847) 228-6850 or fax (847) 228-1856; www.acoem.org.

80th Annual Session-American College of Physicians-American Society of Internal Medicine. April 22–25, 1999. Ernest N. Morial Convention Center, New Orleans. Credit 29 hrs. Contact: ACp-ASIM Customer Service (800) 523-1546, ext. 2600; www.acponline.org.

NOTICE

State Associations should send their CME listings for publication to:

Walter G. Finley, Managing Editor
Western Journal of Medicine
1224 W Main St, Ste 200
Charlottesville, VA 22903-2858

(804) 817-2000 • Fax (804) 817-2020 • wjm@cjp.com

Articles

Antibiotic Resistance in Bacterial Urinary Tract Infections, 1991 to 1997

IRENE E. DYER, MS, MPH; TIMOTHY M. SANKARY, MD, MPH; *and* JO ANN DAWSON, MD, MPH, *Los Angeles, California*

This study assessed changing patterns of antibiotic resistance in *Escherichia coli* urinary tract infections at a university student health center during three periods: the first 6 months each of 1991, 1994, and 1997. Urine culture and sensitivity results were taken from available medical records of female patients having urine cultures during the three periods (1991, *n* = 739; 1994, *n* = 938; 1997, *n* = 863); age and ethnicity were also noted. In *E. coli* isolates (the majority of positive cultures), resistance to four antibiotics changed significantly: ampicillin (30% to 45% to 39%), carbenicillin (29% to 42% to 39%), tetracycline (29% to 40% to 23%), and trimethoprim/sulfamethoxazole (15% to 32% to 15%). The results raise questions regarding the future clinical reliability of several commonly used antibiotics in the treatment of urinary tract infection.

(Dyer IE, Sankary TM, Dawson JA. Antibiotic resistance in bacterial urinary tract infections, 1991 to 1997. West J Med 1998; 169:265–268)

Bacterial infection of the urinary tract is a common health problem in young women.[1] *Escherichia coli* accounts for approximately 80% of uncomplicated cystitis in this group, with *Staphylococcus saprophyticus* reportedly causing another 5%–15%.[2] Treatment regimens for urinary tract infection (UTI) in the outpatient setting have often consisted of trimethoprim-sulfamethoxazole (TMP/SMX) or ampicillin, both of which may become less effective as bacterial resistance to various antimicrobials becomes more common.[2–11] Resistant bacterial strains are emerging and spreading throughout the world, mainly because of the extreme genetic plasticity of the microorganisms themselves, the mobility of the world population, and the heavy selective pressures of antimicrobial use.[10,12]

Increased risk of UTI is found in women who are sexually active, those using diaphragms with spermicide, those who delay postcoital urination, and those with a recent history of urinary tract infection.[13–15] The university health service is an ideal setting for collecting data on a young, sexually active population. A 1993 study[16] of UTI in college women in New York indicated that amoxicillin and the cephalosporins were no longer effective first-line UTI treatments, but that nitrofurantoin and TMP/SMX remained good choices.

At the UCLA Student Health Center, female patients who present with symptoms of UTI are treated empirically with ampicillin or TMP/SMX, after being instructed to collect a clean-catch midstream urine specimen. A urinalysis and urine culture are performed on each specimen. On all urine specimens with pure growth of a known uropathogen, further workup includes identification, colony count, and antimicrobial susceptibility testing. Patients are instructed to return for follow-up treatment if symptoms persist. The policies and practices for obtaining cultures have not changed for the past 7 years.

The aim of this retrospective chart review was to compare the results of urine cultures obtained during three time periods, the first 6 months each of 1991, 1994, and 1997, to evaluate the change in *E. coli* antibiotic resistance over a 6-year period and its potential implications for treatment of UTI.

Methods

Urine culture results were obtained from the medical records of all female patients at the UCLA Student Health Center who had urine cultures performed during January through June of 1991, 1994, and 1997. We analyzed the first culture obtained from each patient within each of the time periods, regardless of result. Information collected included patient's date of birth and race/ethnicity, date of first culture, organisms isolated (if any), colony count, and antibiotic susceptibility results, if performed. If more than one organism was isolated, results were recorded as "mixed culture." We defined a

From the Department of Epidemiology, UCLA School of Public Health (Ms Dyer and Dr Sankary), and the UCLA Student Health Center (Dr Dawson), Los Angeles, California.

Reprint requests to Irene E. Dyer, MS, MPH, L.A. County STD Program, 2615 S. Grand Ave., Room 500, Los Angeles, CA 90007 (e-mail: idyer@deltanet.com).

ABBREVIATIONS USED IN TEXT

TMP/SMX = trimethoprim-sulfamethoxazole
UTI = urinary tract infection.

positive culture as pure growth of a known uropathogen with a colony count of greater than 100,000 colony-forming units per milliliter.

Laboratory testing was performed at the UCLA Student Health Center Laboratory. Identification of Gram-negative organisms and antibiotic susceptibility testing were performed using the Baxter Microscan system (Baxter Diagnostics, McGaw Park, IL), according to the manufacturer's guidelines. The antibiotics tested and the concentrations used to define resistance were as follows: ampicillin, ≥128 µg/ml; amoxicillin/clavulanic acid, >16/8 µg/ml; carbenicillin, >64 µg/ml; cephalothin, >16 µg/ml; ciprofloxacin, >2 µg/ml; nitrofurantoin, >64 µg/ml; tetracycline, ≥128 µg/ml; and TMP/SMX, >2/38 µg/ml. Organisms with "intermediate" levels of resistance were not included in the percentages of resistant organisms. No changes in laboratory or testing methods were made during the study period.

Results

Study Populations: 1991 versus 1994 versus 1997

A total of 790 female patients had urine cultures ordered in the first half of 1991; 51 patient charts were missing or incomplete, leaving 739 (94%) charts from 1991 for analysis. In the first six months of 1994, urine cultures were ordered on 945 women; seven charts were missing or incomplete, leaving 938 (99%) charts to be analyzed from 1994. Medical records from the first half of 1997 were available on all 863 (100%) female patients who had urine cultures.

The study populations in 1991, 1994, and 1997 were similar with respect to age (median age 22.0, 23.0, and 22.3 years, respectively), but ethnicity varied somewhat; an increase in the percentage of Asians (19.1%, 26.7%, and 29.9%) was offset by a decrease in the percentage of whites (53.0%, 44.7%, and 38.4%, respectively).

Culture results were similar between the three populations. In 1991, 1994, and 1997, *E. coli* was the sole isolate in 31%, 33%, and 29% of cultures, respectively; a different single pathogen was isolated in 14%, 11%, and 9%; and a result of no growth, mixed organisms, *Lactobacillus* species, or *Staphylococcus epidermidis* was reported in 55%, 56%, and 63% of cultures.

Positive Cultures

There were 286 positive cultures in the 1991 group (69% *E. coli*, 9% other Gram-negative bacilli, 3% *Staphylococcus saprophyticus*, and 19% other single organisms). In the 1994 patients, 343 had positive cultures (75% *E. coli*, 7% other Gram-negative bacilli, 3% *S. saprophyticus*, and 15% other single organisms). In 1997, 246 patients had positive cultures (81% *E. coli*, 8% other Gram-negative bacilli, 5% *S. saprophyticus*, and 6% other single organisms). The percentage of positive cultures with *E. coli* isolates increased significantly between 1991 and 1997.

TABLE 1.—*Demographic characteristics and E. coli antibiotic resistance in patients with E. coli urinary tract infections*

	1991 (n = 198)	1994 (n = 263)	1997 (n = 208)
Age (%)			
18–21 years	49.0	47.9	48.6
22–25 years	32.8	33.8	37.5
≥26 years	18.2	18.3	13.9
Ethnicity (%)			
White (non-Hispanic)	54.0	41.1	35.6*†
Asian	19.7	33.1	33.6*†
Hispanic	11.6	12.9	17.3
Black	8.6	8.0	5.3
Other	2.0	1.1	5.8
Data missing	4.0	3.8	2.4
Antibiotic resistance (%)			
Ampicillin	30.3	44.9	38.9*†
Amoxicillin/Clavulanic Acid	4.5	1.5	0.5
Carbenicillin	29.3	41.8	38.5*†
Cephalothin	16.7	14.8	15.4
Ciprofloxacin	0.5	0.0	0.0
Nitrofurantoin	0.0	0.0	0.0
Tetracycline	28.8	40.3	22.6‡
Trimethoprim/sulfamethoxazole	14.6	31.9	15.4‡

Statistically significant difference at $P < 0.01$: *1991/1994, †1994/1997.

We further examined the three groups of patients with positive *E. coli* cultures; the results of that comparison are shown in Table 1. The three groups did not differ significantly with respect to age, but the same ethnic differences observed in the total study populations were seen. There was a statistically significant drop in the percentage of white students, with a corresponding increase in the percentage of Asians from 1991 to 1994 and 1997.

Notable differences were apparent in the antibiotic sensitivity results between the 1991, 1994, and 1997 populations. While resistance to amoxicillin/clavulanic acid, ciprofloxacin, nitrofurantoin, and cephalothin did not differ significantly between the three groups, there were significant changes in resistance to the other antibiotics tested. Ampicillin resistance increased from 30% in 1991 to 45% in 1994 ($P < 0.05$), then decreased to 39% in 1997. Carbenicillin resistance increased from 29% in 1991 to 42% in 1994, and decreased slightly to 39% in 1997 ($P < 0.05$). Tetracycline resistance showed a significant increase from 29% in 1991 to 40% in 1994, but then decreased to only 22.6% in 1997. TMP/SMX resistance significantly increased from 14% resistance in 1991 to 31% in 1994, then dropped to 15% in 1997 (Figure 1).

In all three groups, 44% of *E. coli* isolates were sensitive to all tested antibiotics. Another common pattern

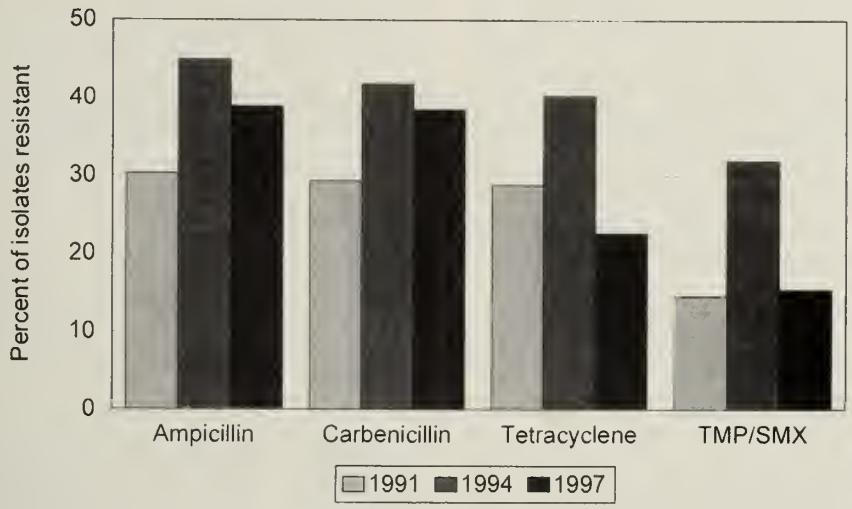


Figure 1.—*E. coli* antibiotic resistance, 1991, 1994, and 1997.

included ampicillin, carbenicillin, and tetracycline resistance occurring together in 17%, 24%, and 15% of isolates in 1991, 1994, and 1997, respectively.

Discussion

The increasing resistance of *E. coli* organisms in UTI to commonly used antibiotics was demonstrated in the first 3 years of this study, with four antibiotics (ampicillin, carbenicillin, tetracycline, and TMP/SMX) showing a marked increase in resistance over the first 3-year period. In the following 3 years, however, the trend did not continue. Resistance to ampicillin and carbenicillin leveled off (1994/1997 differences were not statistically significant), and tetracycline and TMP/SMX both decreased in resistance to return approximately to 1991 levels.

The reasons for the diminishing resistance to two commonly used antibiotics from 1994 to 1997 may include a change in usage by providers. Results of a recently published Finnish study[17] of erythromycin resistance in group A Streptococci strongly suggest that a widespread reduction in the use of certain antibiotics may be effective in lowering the frequency of resistant organisms in the population. In an earlier study, Ballow and Schentag[3] reported a decrease in *E. cloacae* resistance to ceftazidime in hospitalized patients following restricted usage of the drug. Prescription drug utilization data from the past 6 years at the UCLA Student Health Center are not available, indicating a need for further studies examining the correlation between antibiotic usage and organism resistance.

The two most commonly used antibiotics for treatment of UTI at the UCLA Student Health Center are ampicillin and TMP/SMX. In 1994, ampicillin was ineffective against 45% of *E. coli* isolates and TMP/SMX was ineffective against 32% of *E. coli* isolates. In 1997, TMP/SMX resistance dropped to 15% and ampicillin resistance was 39%. Further analysis shows that 77 of 263 isolates in 1994 (29%) were resistant to both ampicillin and TMP/SMX, but in 1997 only 28 (13%) of isolates were resistant to both antibiotics. Patterns of resistance as seen here may be due to single genetic mutations in the *E. coli* organisms.[9] No *E. coli* isolates were found to be resistant to every tested antibiotic. However, factors such as toxicity, limited spectrum, and high cost may make some antibiotic choices undesirable.

It is interesting to note that resistance to nitrofurantoin was nonexistent in all three periods. Years ago, this drug was commonly prescribed for UTI because it concentrates in the urine, where it is most effective. It has fallen out of favor in recent years, perhaps due to side effects and the development of new bacteriocidal antibiotics. However, from our results, it appears that nitrofurantoin should be reexamined as a first-line drug for UTI.

Since urinalysis results were not collected as part of this study, we do not know what proportion of patients whose urines were cultured or had positive cultures also had pyuria or other indications that the *E. coli* isolates evaluated were clinically significant.

We did not find age to be a factor in the results. Older females with presumably greater opportunity for antibiotic exposure and resistance did not have any more resistance than younger women. It seems that resistant urinary pathogens are widely distributed throughout the population. The differences in ethnic composition in the three groups most likely reflect the population of the UCLA student body as a whole (in recent years, an increasing number of Asian students have enrolled at the University).

Conclusion

Bacteria with antimicrobial resistance are associated with more morbidity, mortality, and cost (as measured by hospitalization and death rates) than are their drug-susceptible counterparts.[18] It is important, therefore, to examine treatment strategies with attention to preventing increased bacterial resistance, as well as to effective treatment and cost containment.

This study indicates a need for re-evaluation of current treatment protocols at the UCLA Student Health Center. The use of ampicillin as an empirical first choice for UTI is clearly not indicated, since nearly 40% of all *E. coli* infections were resistant to this drug. TMP/SMX may be a better choice, but if usage increases, it may not remain satisfactory. It continues to be advisable to obtain a urine specimen for culture on every patient presenting with UTI symptoms, so as to follow-up on incomplete or ineffective treatment.

Further studies that examine the relationships among clinical symptoms, antibiotic usage, organism resistance, and clinical outcomes would be valuable to determine appropriate treatment strategies.

Acknowledgments

The authors gratefully acknowledge the contribution of the following: Kahan Allen, Lissette Almodovar, Jermaine Augustus, Joy Collins, Carmel Comendador, David Daukas, Jamila Dawson, Khalid Dawson, Maria Lara, Cynthia Whang, Roy Yaari, Ken Yemat, and Lee Borenstein.

REFERENCES

1. Stamey TA. Pathogenesis and Treatment of Urinary Tract Infections. Baltimore: Williams & Wilkins; 1980

2. Stamm WE, Hooton TM. Management of urinary tract infections in adults. N Engl J Med 1993; 329:1328–1334

3. Ballow CH, Schentag JJ. Trends in antibiotic utilization and bacterial resistance. Report of the National Nosocomial Resistance Surveillance Group. Diagn Microbiol Infect Dis 1992; 15:37S–42S

4. Emerging resistance in uropathogens: its impact on management of acute cystitis in women. In Baum N, Stratton CW (Eds): Acute Cystitis: A Special Report. Consensus Conference Proceedings. New York: McGraw-Hill; 1994

5. Alon U, Davidai G, Berant M, Merzbach D. Five-year survey of changing patterns of susceptibility of bacterial uropathogens to trimethoprim-sulfamethoxazole and other antimicrobial agents. Antimicrob Agents Chemother 1987; 31:126–128

6. Cunney RJ, McNally RM, McNamara EM, Al-Ansari N, Smyth EG. Susceptibility of urinary pathogens in a Dublin teaching hospital. Irish J Med Sci 1992; 161:623–625

7. Harnett N. Transferable high-level trimethoprim resistance among isolates of *Escherichia coli* from urinary tract infections in Ontario, Canada. Epidemiol Infect 1992; 109:473–481

8. Heikkila E, Renkonen OV, Sunila R, Uurasmaa P, Huovinen P. The emergence and mechanisms of trimethoprim resistance in *Escherichia coli* isolated from outpatients in Finland. J Antimicrob Chemother 1990; 25:275–283

9. Jacoby GA, Archer GL. New mechanisms of bacterial resistance to antimicrobial agents. N Engl J Med 1991; 324:601–610

10. Kunin CM. Resistance to antimicrobial drugs—a worldwide calamity. Ann Int Med 1993; 118:557–561

11. Neu HC. The crisis in antibiotic resistance. Science 1992; 257:1064–1073

12. Cohen ML. Epidemiology of drug resistance: Implications for a post-antimicrobial era. Science 1992; 257:1050–1055

13. Remis RS, Gurwith MJ, Gurwith D, Hargrett-Bean NT, Layde PM. Risk factors for urinary tract infection. Am J Epidemiol 1987; 126:685–694

14. Strom BL, Collins M, West SL, Kreisberg J, Weller S. Sexual activity, contraceptive use, and other risk factors for symptomatic and asymptomatic bacteriuria. Ann Int Med 1987; 107:816–823

15. Foxman B, Frerichs RR. Epidemiology of urinary tract infection. I. Diaphragm use and sexual intercourse. Am J Public Health 1985; 75:1308–1313

16. Ansbach RK, Dybus KR, Bergeson R. Uncomplicated *E. coli* urinary tract infection in college women: a retrospective study of *E. coli* sensitivities to commonly prescribed antibiotics. College Health 1995; 43:183–185

17. Seppala H, Klaukka T, Vuopio-Varkila J, Muotiala A, Helenius H, Lager K, Huovinen P. The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A Streptococci in Finland. N Engl J Med 1997; 337:441–446

18. Patton JP, Nash DB. Urinary tract infection: economic considerations. Med Clin North Am 1991; 75:495–513

19. Gruneberg RN. Changes in the antibiotic sensitivities of urinary pathogens, 1971–1989. J Antimicrob Chemother 1990; 26(Suppl F):3–11

Articles

Prevention Services in Primary Care:

Taking Time, Setting Priorities

MICHAEL RAFFERTY, MD, *Atlanta, Georgia*

Preventive services are delivered at rates far below recommended levels. Although lack of time has frequently been cited as an important factor, little is known about how much time primary care clinicians devote to prevention and how they prioritize that time. Work sampling was used to estimate the proportion of time spent on prevention during routine care of patients by primary care clinicians in two hospital-based clinics serving indigent patients. Clinicians were prompted by computer at random intervals to describe their current activity and, if the activity was prevention-related, to choose the specific activity from a list modified from the U.S. Preventive Services Task Force (USPSTF) recommendations. Proportions of time spent on prevention overall and by specific prevention activity were calculated, and the association between USPSTF ratings of specific prevention activities and proportion of time spent on those activities was examined using Kendall's Tau. Clinicians in these clinics spent just 11% of their time on prevention, or about 7 minutes per patient per year. Screening for just two diseases, breast cancer and cervical cancer, accounted for half of all prevention-related activity. There was no overall relation found between proportion of time by specific prevention activity and USPSTF ratings. Thus, the primary care clinicians spent little time on prevention and did not apportion that time according to USPSTF recommendations. If these results are representative, time constraints in actual practice may be too severe to deliver the full range of preventive services suggested by USPSTF.

(Rafferty M. Prevention services in primary care: taking time, setting priorities. West J Med 1998; 169:269–275)

While primary care physicians generally agree with published guidelines about prevention,[1,2] most preventive services are delivered at rates far below recommended levels.[3–6] A number of studies point to lack of time as an important reason,[7–9] but little is known about how primary care practitioners spend their time with patients or how much time they devote to prevention. The extensive recommendations published by groups like the U.S. Preventive Services Task Force (USPSTF)[10] may be too time-consuming for primary care practice, an issue that has not been well studied. Some idea of how much time is currently devoted to prevention in primary care and how that time is spent would contribute to our understanding of the way time constraints affect the delivery of clinical preventive services.

In previous studies, the proportion of time devoted to prevention has varied depending on how it was measured. In surveys, primary care physicians estimate that 23%–32% of their patients' visits are for prevention,[11,12] and that they spend 17%–35% of their time with patients performing prevention activities.[13,14] The authors of those and other studies acknowledge, however, that in surveys, physicians probably overestimate the amount of preventive care they provide.[8,15,16] Studies on prevention time using objective methods such as direct observation are few and limited in scope. One study of cancer screening in primary care practice found that physicians spent an average of 28.7 minutes to perform a "cancer-related checkup" requested by actors posing as patients.[17] Other prevention activities were not studied. In an analysis of audiotaped visits to primary care clinicians by patients with chronic diseases, health promotion discussions occurred in 53% of the visits and lasted a mean of 4.5 minutes,[18] although much of that counseling was probably devoted to prevention of complications of chronic disease rather than primary prevention. No study to date has directly and objectively addressed the question of how much time is spent on the whole range of prevention activities in routine primary care practice.

From the Department of Family and Preventive Medicine, Emory University School of Medicine, Atlanta, Georgia.

Reprint requests to Michael Rafferty, MD, Department of Family and Preventive Medicine, Emory University School of Medicine, 69 Butler St SE, Atlanta, GA 30303 (e-mail: mraffert@fpm.eushc.org).

The purpose of this study was to employ a different measurement technique, work sampling, to estimate the proportion of time primary care clinicians devote to the full range of prevention activities. Work sampling has not been used in past studies of prevention activity and has several advantages over other techniques. It avoids the recall bias that may inflate estimates of prevention time using survey methods, and it is preferable to direct observation techniques in taking account of activities of short duration or those that are blended in with other activities, as is typical in primary care.[18] Direct observation is also intrusive and expensive. USPSTF guidelines, which are both complete and well-known, were used as a comprehensive listing of all possible prevention activities that primary care clinicians might be expected to know about and perform. In addition to making an estimate of prevention time, this study also reports the kinds of prevention services delivered and tests the hypothesis that the clinicians spent proportionately more time on prevention services highly rated by USPSTF than on those less highly rated.

Methods

Study Setting and Subjects

Fourteen primary care clinicians (7 general internists, 3 family practitioners, 3 nurse practitioners, and 1 physician's assistant) participated in the study. The participants were university faculty and staff of a large urban public hospital who practice adult primary care in two neighborhood health centers operated by the hospital. Patients seen in these clinics are largely African-American, poor, and uninsured. Approximately 30,000 patient visits are made to the two centers annually, and clinicians see an average of three to four patients per hour. Patients are charged for care using a sliding fee scale, and because of poverty, lack of health insurance, and scarcity of other local clinicians, most patients receive all of their primary care from these clinics. Most of the preventive care is delivered by the clinicians rather than support staff, with the exception of high blood pressure screening and the actual administration of vaccines (which requires a clinician's order). At both sites, clinicians use a clinical computerized database in routine care of their patients, directly entering and modifying patient demographic and utilization data and *International Classification of Diseases, Ninth Revision* (ICD-9)–coded problem lists at personal workstations in each office. The clinics under study were chosen because of patient volume and because their physical layout made possible the use of an audible prompt (a computer beep), explained below. All clinicians in these clinics were invited to participate, and all agreed. Participants were informed that the purpose of the study was to measure time spent in prevention but were blinded to the hypothesis that more prevention time would be devoted to highly rated USPSTF-recommended services. All participants signed informed consent, which included the purpose of the study, a copy of the prevention activities to be measured, and provisions for confidentiality and withdrawal from the study. The study protocol was approved by the Emory University School of Medicine Human Investigations Committee.

Work Sampling

In work sampling, after a typology of all possible activities is created, a subject is repeatedly observed, and his or her actions at the time of a sample observation are classified according to the typology. The proportion of time spent on any activity listed in the typology is the proportion of distinct observations that are classified as that activity.[19] If, for example, talking and listening are the only possible activities in a study of two people conversing, and a study subject is observed talking in three of 10 observations and listening in the remaining seven, then the subject has spent 30% of his or her time talking and 70% listening.

During the 6-month study period, the computers in each office were programmed to emit a beep at random times once per hour between 10 a.m. and 4 p.m., the period of peak activity in the clinics. More frequent sampling was thought by the participants to be too intrusive. Clinicians were asked to note their current activity at the time of the beep and to respond as quickly as possible but without interrupting their current activity. If the clinician was out of the room at the time of the beep and was therefore unaware of the exact time it sounded, the clinician was instructed upon his or her return to report the main activity while out of the room. Clinicians were also asked in every case to confirm or correct an identifier of the patient for whom the activity was performed. The observation was later matched to demographic and clinic utilization data about the patient, available for 94% of all observations (3,122 of 3,336). The remaining 6% of observations either lacked identifiers or were made on patients not entered in the database.

Data Collection

After sounding the beep, the computer presented a series of branching screens designed to determine what the participant was doing at the precise moment of the sound (Figure 1). The screens followed a typology of primary care activities designed with feedback from participants before the study to be clear and comprehensive and to minimize the time required to respond (generally less than 15 seconds per sampled observation, and frequently less for replies that quickly branched to an endpoint). Following the USPSTF approach, which is concerned with primary prevention and screening for asymptomatic disease, prevention activities were defined as any screening, counseling, or chemoprophylaxis activity to detect or prevent the diseases and conditions explicitly listed by USPSTF[20] (Figure 1). Questions about prenatal care, which is not delivered in these clinics, were omitted from the USPSTF scheme. Activities related to established problems, such as diabetes, or evaluation of symptomatic but as yet undiagnosed problems, such as a breast mass, were not counted as prevention activities. Participants chose

Figure 1.—The questions below were presented to participating clinicians at randomly chosen intervals. Branch and end points were automatically followed by computer. The final set of responses was displayed for review and revision by the participant before an observation was added to the data set.

Is your current activity
1. Personal?
2. Administrative?
3. Teaching?
4. Triage?
5. Patient-related?

What kind of patient contact is this?
1. Patient present in clinic
2. Telephone contact with patient
3. Neither in-clinic nor telephone contact

Which of the following best describes your current activity?
1. History
2. Physical exam
3. Counseling
4. Procedure
5. Interpretation (lab, ECG, etc.)
6. Chart
7. Computer use
8. Forms, letters, etc.

Is this activity essentially
1. Diagnosis/treatment/management?
2. Screening/prevention?

If essentially screening/prevention, which of the following best describes the activity?
1. Screening (branch 1)
2. Counseling (branch 2)
3. Immunization/chemoprophylaxis (branch 3)

Screening

A. Vascular diseases: screening for
1. Asymptomatic coronary artery disease
2. High blood cholesterol
3. Hypertension
4. Cerebrovascular disease
5. Peripheral arterial disease

B. Neoplastic diseases: screening for
6. Breast cancer
7. Colorectal Cancer
8. Cervical Cancer
9. Prostate Cancer
10. Lung Cancer
11. Skin Cancer
12. Testicular Cancer
13. Ovarian Cancer
14. Pancreatic Cancer
15. Oral Cancer

C. Metabolic disorders: screening for
16. Diabetes
17. Thyroid disease
18. Obesity
19. Phenylketonuria

D. Infectious diseases: screening for
20. Hepatitis B
21. Tuberculosis
22. Syphilis
23. Gonorrhea
24. HIV infection
25. Chlamydia
26. Genital herpes simplex
27. Bacteriuria, hematuria, and proteinuria

E. Hematologic disorders: screening for
28. Anemia
29. Hemoglobinopathies
30. Lead toxicity

F. Ophthalmologic and otologic disorders: screening for
31. Diminished visual acuity
32. Glaucoma
33. Hearing impairment

H. Musculoskeletal disorders: screening for
40. Postmenopausal osteoporosis
41. Risk of low back injury

I. Mental disorders and substance abuse: screening for
42. Dementia
43. Abnormal bereavement
44. Depression
45. Suicidal intent
46. Violent injuries
47. Alcohol and other drug abuse

Counseling
1. To prevent tobacco use
2. Exercise
3. Nutritional
4. To prevent motor vehicle injuries
5. To prevent household and environmental injuries
6. To prevent HIV infections and other sexually transmitted diseases
7. To prevent unintended pregnancy
8. To prevent dental disease

Immunization/chemoprophylaxis
1. Childhood immunizations
2. Adult immunizations
3. Postexposure prophylaxis
4. Estrogen prophylaxis
5. Aspirin prophylaxis

answers by pointing and clicking with a mouse, and the program performed the proper branching according to their responses. After reaching an endpoint, participants reviewed their answers and could restart the series of screens from any point at which they wished to change an answer, again being led through the proper sequence of questions. Participants logged on to the system immediately after arrival each day using a unique ID and

TABLE 1. *Characteristics of 2,826 Patients Seen in the Primary Care Clinics During the Study Period*

Race	93% African-American
Sex	76% female
Age (years)	
<45	27%
45–65	39%
>65	34%
Income	56% poor[1]
Health insurance	
Uninsured	37%
Medicare	33%
Medicaid	18%
Other	12%
Most common medical problems	
Hypertension	65%
Osteoarthritis	28%
High blood cholesterol	27%
Obesity	26%
Diabetes	23%
Current smoking	18%
Anemia	8%
Low back pain	7%
Clinic visits in the preceding year (mean)	3.2

[1]Family income less than the federal poverty level.

TABLE 2. *Activities of Primary Care Clinicians*

Activity	*n*	*Percent (95% CI)*[1,2]
Non–patient-related[3]	1227	26.9 (25.6–28.2)
Patient-related	3336	73.1 (71.8–74.4)
Total	4563	100%
Diagnosis/management/treatment	2981	89.4 (88.3–90.4)
Screening/prevention	355	10.6 (9.6–11.7)
Total	3336	100%
Screening	242	68.2 (63.4–73.0)
Counseling	61	17.2 (13.3–21.1)
Immunization/Chemoprophylaxis	52	14.6 (10.9–18.3)
Total	355	100%

[1]Column entries are observations.
[2]95% CI are calculated for percentages (proportions) as described in Methods using total observations in each category (4563, 3336, or 355) as the denominator.
[3]Non–patient-related activities include administration, teaching, triage, and personal activities.

password; they were prompted for observations only when they were present in the clinic. To ensure that activities such as administrative or personal tasks (e.g., lunch) did not affect prevention time estimates, the first screen separated patient-related activities from such non-care activities; only time spent in actual patient care was analyzed in this study.

Data Analysis

Confidence limits for the proportion of time spent in any activity were calculated using the standard error of a proportion.[21] Prevention activities were divided into categories that corresponded to those used by USPSTF to assign "strength of recommendation" ratings.[10] This scheme, which specifies both an activity (e.g., screening for breast cancer) and age- and sex-specific target group (e.g., women 50–70 years old) considers the quality of evidence in support of the activity, assigning a rating from highest quality (A) to lowest (E). Categorized this way, 17 activities accounted for 95% of all prevention activities observed; the remaining activities were observed less than 0.1% of the time spent with target patients. In measuring the proportion of time spent in each of these categories, only observations made on the target group were used as numerator (prevention-related observations) and denominator (both prevention and non-prevention observations). These 17 common prevention activities were ranked by their strength of recommendation ratings, and the association between those ratings and the proportion of time spent on various activities was calculated as Kendall's tau. These analyses are reported for the 94% of patient-related activity observations that could be linked to demographic and utilization data from the general database.

Results

Observations were made during the care of 2,826 patients (Table 1). The patients were predominantly African-American (93%), female (76%), poor (56% with incomes below the federal poverty level), and uninsured (37%) or receiving Medicare or Medicaid (33 and 18%, respectively). On average, they had visited the clinic 3.2 times in the 12 months preceding their last visit during the study period. The most common medical problem was hypertension (65%), and 20–30% of the patients also had osteoarthritis, high blood cholesterol, obesity, or diabetes.

A total of 4,563 observations were made (Table 2). In 3,336 (73%), the clinician was involved in direct patient care. Of the 3,336 patient care observations, 355 (10.6%) were made when the clinician was involved in prevention activities. The remainder were made during diagnosis, treatment, and management of established or symptomatic problems. The clinicians in this study, therefore, spent about 11% of their patient care time on prevention. Most of the preventive activity consisted of screening for asymptomatic disease (68%), while the rest was nearly evenly divided between counseling (17%) and immunization and chemoprophylaxis (15%). Most of the screening activity was for neoplastic disease (207 of 242 observations, 86%); screening for two diseases, breast cancer and cervical cancer, accounted for 73% of screening activity and 50% of all prevention activity (Table 3). Counseling activities primarily involved nutrition or smoking practices (35 of 61 observations, 53%), and immunization and chemoprophylaxis activity consisted almost entirely of adult immunization (46 of 52 observations, 89%).

TABLE 3. *Prevention Activities of Primary Care Clinicians*

Activity	*n*	*Percent (95% CI)*[1]
Screening		
Neoplastic diseases		
Breast cancer	106	29.9 (25.1–34.6)
Cervical cancer	70	19.7 (15.6–23.9)
Colorectal cancer	13	3.7 (1.7–5.6)
Other cancer[2]	18	5.1 (2.8–7.4)
Vascular diseases	22	6.2 (3.7–8.7)
Other[2]	13	3.7 (1.7–5.6)
Screening total	242	68.2 (63.4–73.0)
Counseling		
Nutrition	25	7.0 (4.4–9.7)
Tobacco Use	10	2.8 (1.1–4.5)
Exercise	8	2.3 (0.7–3.8)
HIV/STD	7	2.0 (0.5–3.4)
Other[2]	11	3.1 (1.3–4.9)
Counseling total	61	17.2 (13.3–21.1)
Immunization/chemoprophylaxis		
Adult immunization	46	13.0 (9.5–16.5)
Other[2]	6	1.7 (0.3–3.0)
Immunization/chemoprophylaxis total:	52	14.6 (10.9–18.3)
Total	355	100%

[1]Column entries are observations.
[2]See Fig. 1 for a full list of diseases or activities.

TABLE 4. *Prevention Effort and USPSTF Ratings*

Preventive Activity	*Target Group*	*Rating*	*% Time*
Screening for breast cancer	Women ages 50–70	A	5.4
Screening for cervical cancer	Women[1]	A	3.7
Screening for breast cancer	Women age <50 or >70	C	3.4
Adult immunization	All[2]	B	2.1
Screening for prostate cancer	Men age >50	D	1.8
Counseling on tobacco use	All[3]	A	1.3
Counseling on prevention of HIV/STDs	All age <45	C	0.9
Counseling on nutrition	All	C	0.8
Counseling on unintended pregnancy	All age <45[4]	B/C	0.6
Screening for colorectal cancer	All age >50	B	0.5
Screening for HIV	All age <45	A	0.3
Screening for cholesterol	All[5]	B/C	0.3
Counseling on exercise	All	C	0.3
Screening for hypertension	All[6]	A	0.2
Screening for ovarian cancer	Women	D	0.2
Counseling on preventing injury	All	B/C	0.2
Estrogen prophylaxis	Women age >50	B	0.1

Preventive activities shown account for 95% of all prevention effort. Target groups are USPSTF categories for each preventive activity. B/C is a combined rating when the data did not allow separation into groups with separate B or C ratings. Percent time is calculated separately for each target group, and thus does not add to the same 10.6% total prevention percent time given in Table 2. Kendall's Tau = 0.19.
[1]Women with history of hysterectomy excluded.
[2]Age >65 and those with diabetes, heart disease, chronic obstructive lung disease, chronic renal failure, or hemoglobinopathy.
[3]All tobacco users.
[4]Women with history of hysterectomy or tubal ligation excluded.
[5]Those with established lipid disorder excluded.
[6]Those with established hypertension excluded.

Table 4 demonstrates that in this study, there was little relationship between USPSTF strength of recommendation ratings and proportionate time spent on various prevention activities (Kendall's Tau = 0.19). While breast cancer screening for 50–70-year-old women and cervical cancer screening receive USPSTF's highest recommendations and were the most common prevention activities in this study, some other highly recommended services were infrequent (e.g., HIV and hypertension screening). Also, several not-recommended services (screening for prostate cancer in men and breast cancer in women younger than 50) were nonetheless frequent.

Discussion

Using a work sampling methodology and a classification of prevention activities that follows USPSTF categories, this study found that clinicians in one primary care setting spent about 11% of their time with patients on prevention activities, primarily screening for two diseases, breast cancer and cervical cancer. The patients in this study made an average of 3.2 visits to their primary care clinician in the year before the study, almost all of which were illness visits, since few of these patients come solely for prevention. Because visits in these clinics are scheduled to last 20 minutes, about 7 minutes might be available for prevention in a year (11% of 64 minutes).

Other work has shown that on average, Americans see their physician 2.7 times per year for 17 minutes at a time, amounting to just 46 minutes per year.[22] If the results of this study are representative, this translates to just 5 minutes for prevention. Women, whites, and older patients make more frequent and slightly longer visits, but for patients less than 75 years old, these results predict no more than a total of 9.5 minutes per year for prevention.[22] This amount of time is probably insufficient for the delivery of a comprehensive range of prevention services. USPSTF specified 60 target conditions for prevention and 169 age- and sex-specific preventive services in their first report,[20] and even more in their second.[10] In one study of adult ambulatory patients, a computer-based algorithm of 1989 USPSTF rules based on age, sex, and specific risks generated an average of 24.5 recommendations for prevention services per patient,[23] an impossible task to complete in just 10 minutes a year. The time spent on prevention in this study was enough to screen 77% of 50–70-year-old women for breast cancer (data not shown) and 77% of all women for cervical cancer, but this required half of the prevention time spent by these clinicians. Rates for other preventive services that could be measured, such as vaccination of those older than 65 years against pneumococcus (18%) and annually against influenza (25%),

as well as tetanus/diphtheria booster administration (10%), were low, suggesting that the other half of prevention time was spread thinly across these activities and was a constraint on completion rates.

These estimates must be interpreted cautiously. Hospital-based clinics staffed by medical school faculty whose patients are poor, uninsured, and African-American, are not representative of all primary care practices; there may be greater emphasis on prevention in other settings. The group of practitioners studied is small, increasing the chance that the results may have been influenced by a few clinicians with atypical attitudes and knowledge about prevention. Some of the same patients studied here were also seen in specialty clinics of the hospital, and the amount of preventive care delivered by doctors in those clinics was not measured (although it was probably small). Clinicians may have misclassified their activities, although at the outset of the study they were given explicit instructions about which activities were prevention-related. There were no differences over time in the distribution of any clinician's answers, nor was any clinician atypical in his or her answers, suggesting that each understood the questions and answered consistently. Believing that prevention is socially desirable, respondents may have overestimated their prevention activities, although this would mean that the true proportion of prevention time is even less than 11%. Finally, the estimates derived here are relevant only to prevention as defined by USPSTF, which confined its attention to primary prevention and screening for asymptomatic disease, plus chemoprophylaxis.

The lack of a relationship between USPSTF strength of recommendation ratings and the proportion of time devoted to them may have several possible explanations. Practitioners may misunderstand or be ignorant of guideline recommendations,[24,25] or they may simply disagree with them.[26] There are still many controversial areas in prevention, such as prostate cancer screening,[27] and the clinicians in this study may have made decisions about the value of certain prevention activities based on sources other than USPSTF. This study did not measure the differences in the amount of time needed to perform a given prevention task. If, for example, screening for cervical cancer (3.7% of time with the eligible group from Table 4) takes three times as long as counseling about tobacco use (1.3% of time with the eligible group from Table 4), then approximately the same number of eligible women would have been screened for cervical cancer as smokers counseled to quit smoking, although by Table 4 the relative effort appears far different.

Patient-related factors may also explain the lack of correspondence between USPSTF strength of recommendation ratings and the proportion of time devoted to specific prevention activities. Poor patients are less likely to seek preventive services,[28] and the clinicians in this study may have been influenced by their patients' values when choosing which prevention services, if any, to emphasize. Additionally, most patients treated here were African-Americans, who have a higher risk of heart disease, hypertension, diabetes, prostate cancer, and HIV infection[29] but a lower risk of osteoporosis[30] and breast cancer[31] than other racial groups. The clinicians may have considered this risk profile sufficiently different from that of other Americans to justify a different emphasis in prevention. Furthermore, the preventive services given priority by these clinicians would have depended on the kinds of medical problems common in these clinics. Many patients have established cardiovascular disease, hypertension, and lipid disorders, for example, and are not candidates for screening. Finally, the most common preventive activities in Table 4, breast and cervical cancer screening and adult immunization, are among the few preventive services reimbursed by Medicare,[32] and costs to patients and to the hospital may have played a role.

While many factors have been cited to account for failure to deliver prevention services,[33] this study reaffirms that time is an important one. These findings support the concept of the prevention-related annual visit, which can average almost 30 minutes,[14,17] far exceeding the annual time spent on prevention estimated here. There is evidence that this approach is associated with more complete delivery of preventive services than can be accomplished during illness visits.[12,25,34,35] Future studies should address the generalizability of these findings and whether time constraints or attitudes about prevention are responsible for the small proportion of time devoted to prevention found in this study. If time is similarly constrained in other settings, USPSTF and others may wish to consider whether comprehensive prevention is a feasible goal.

REFERENCES

1. Weingarten S, Stone E, Hayward R, Tunis S, Pelter M, Huang HK. The adoption of preventive care practice guidelines by primary care physicians: do actions match intentions? J Gen Intern Med 1995; 10:138–144

2. Stange KC, Kelly R, Chao J, et al. Physician agreement with US Preventive Services Task Force recommendations. J Fam Pract 1992; 34:409–416

3. Fielding JE, Cumberland WG, Pettitt L. Immunization status of children of employees in a large corporation. JAMA 1994; 271:525–530

4. Centers for Disease Control and Prevention. Examinations for oral cancer—United States, 1992. MMWR 1994; 43:198–200

5.Centers for Disease Control and Prevention. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1996; 45:RR-5

6. Fox SA, Murata PJ, Stein JA. The impact of physician compliance on screening mammography for older women. Arch Intern Med 1991; 151:50–56

7. Kottke TE, Brekke ML, Solberg LI. Making "time" for preventive services. Mayo Clin Proc 1993; 68:785–791

8. McPhee SJ, Richard RJ, Sulcus SN. Performance of cancer screening in a university general internal medicine practice: comparison with the 1980 American Cancer Society guidelines. J Gen Intern Med 1986; 1:275–281

9. Spitz MR, Chamberlain RM, Side JG, Figure JJ. Cancer prevention practices among Texas primary care physicians. J Cancer Educ 1992; 7:55–60

10. U.S. Preventive Services Task Force. Guide to clinical preventive services. Report of the U.S. Preventive Services Task Force. 2nd ed. Baltimore, MD: Williams & Wilkins; 1995

11. Rosen MA, Logsdon DN, Demak MM. Prevention and health promotion in primary care: baseline results on physicians from the INSURE Project on Lifecycle Preventive Health Services. Prev Med 1984; 13:535–548

12. Osborn EH, Bird JA, McPhee SJ, Rodnick JE, Fordham D. Cancer screening by primary care physicians. Can we explain the differences? J Fam Pract 1991; 32:465–471

13. Julnes TE, Baker TA. Family practice and internal medicine office fees: an analysis of charge differences. J Fam Pract 1993; 37:35–43

14. Luckmann R, Melville SK. Periodic health evaluation of adults: a survey of family physicians. J Fam Pract 1995; 40:547–554

15. Lewis CE, Clancy C, Leake B, Schwartz JS. The counseling practices of internists. Ann Intern Med 1991; 114:54–58

16. Montano DE, Phillips WR. Cancer screening by primary care physicians: a comparison of rates obtained from physician self-report, patient survey, and chart audit. Am J Public Health 1995; 85:795–800

17. Camey PA, Dietrich AJ, Freeman DH Jr, Mott LA. The periodic health examination provided to asymptomatic older women: an assessment using standardized patients. Ann Intern Med 1993; 119:129–135

18. Russell NK, Roter DL. Health promotion counseling of chronic-disease patients during primary care visits. Am J Public Health 1993; 83:979–982

19. Finkler SA, Knickman JR, Hendrickson G, Lipkin M Jr, Thompson WG. A comparison of work-sampling and time-and-motion techniques for studies in health services research. Health Serv Res 1993; 28:577–597

20. The U.S. Preventive Services Task Force. Guide to clinical preventive services: an assessment of 169 interventions. Report of the U.S. Preventive Services Task Force. 1st ed. Baltimore, MD: Williams & Wilkins; 1989

21. Glantz S. Primer of Biostatistics. New York: McGraw-Hill; 1981

22. Schappert SM. National Ambulatory Medical Care Survey: 1991 summary. Vital & Health Statistics—Series 13: Data From the National Health Survey 1994; 1–110

23. Medder JD, Kahn NB Jr, Susman JL. Risk factors and recommendations for 230 adult primary care patients, based on U.S. Preventive Services Task Force guidelines. Am J Prev Med 1992; 8:150–153

24. Shea S, Gemson DH, Mossel P. Management of high blood cholesterol by primary care physicians: diffusion of the National Cholesterol Education Program Adult Treatment Panel guidelines. J Gen Intern Med 1990; 5:327–334

25. Stange KC, Fedirko T, Zyzanski SJ, Jaen CR. How do family physicians prioritize delivery of multiple preventive services? J Fam Pract 1994; 38:231–237

26. Zyzanski SJ, Stange KC, Kelly R, Flocke S, Shank JC, Chao J, et al. Family physicians' disagreements with the US Preventive Services Task Force recommendations. J Fam Pract 1994; 39:140–147

27. Mettlin C, Jones G, Averette H, Gusberg SB, Murphy GP. Defining and updating the American Cancer Society guidelines for the cancer-related checkup: prostate and endometrial cancers. Ca: a Cancer Journal for Clinicians 1993; 43:42–46

28. Elnicki DM, Morris DK, Shockcor WT. Patient-perceived barriers to preventive health care among indigent, rural Appalachian patients. Arch Intern Med 1995; 155:421–424

29. Public Health Service. Healthy People 2000: National Health Promotion and Disease Prevention Objectives. Washington, DC: U.S. Department of Health and Human Services, DHHS Pub No 91-50212; 1990

30. Ross PD. Osteoporosis. Frequency, consequences, and risk factors. Arch Intern Med 1996; 156:1399–1411

31. Moormeier J. Breast cancer in black women. Ann Intern Med 1996; 124:897–905

32. Schauffler HH. Disease prevention policy under Medicare: a historical and political analysis. Am J Prev Med 1993; 9:71–77

33. Walsh JM, McPhee SJ. A systems model of clinical preventive care: an analysis of factors influencing patient and physician. Health Educ Q 1992; 19:157–175

34. Conry CM, Main DS, Miller RS, Iverson DC, Calonge BN. Factors influencing mammogram ordering at the time of the office visit. J Fam Pract 1993; 37:356–360

35. Williams RB, Boles M, Johnson RE. Use of prostate-specific antigen for prostate cancer screening in primary care practice. Arch Fam Med 1995; 4:311–315

Articles

Vancomycin-Resistant Enterococcal Colonization in Nonhospitalized HIV-Infected Patients

VINOD K. DHAWAN, MD; RONALD NACHUM, PhD; NIMEC BHAT, BS; LAURIE TOLBERT, RN, BS, PHN; *and* MANJU AGRAWAL, MD; *Los Angeles, California*

We studied fecal colonization with vancomycin-resistant enterococci (VRE) in 89 HIV-infected nonhospitalized patients ages 24 to 62 years, including 70 (79%) men (including 41 homosexual and 5 bisexual men) and 19 (21%) women. Of the 89 patients, 61 (69%) were black, 25 (28%) Hispanic, and 3 (3%) white; 53 (60%) had history of ongoing or recent antibacterial therapy with trimethoprim/sulfamethoxazole (29), clarithromycin (18), amoxicillin (7), ofloxacin (3), and metronidazole, doxycycline, dicloxacillin, and cephalexin (1 each). VRE were not isolated from any of the patients studied.

(Dhawan VK, Nachum R, Bhat N, Tolbert L, Agrawal M. Vancomycin-resistant enterococcal colonization in nonhospitalized HIV-infected patients. West J Med 1998, 169:276–279)

The prevalence of vancomycin-resistant enterococci (VRE) has rapidly escalated in hospitals across the United States, from 0.4% in 1989 to 10% in 1995.[1] VRE are generally considered to be nosocomial pathogens, but several European studies have documented their prevalence in the fecal flora of healthy nonhospitalized people[2] and in community-acquired infections.[2–5] In the United States, attention has focused on the epidemiology of VRE mainly in hospitals, whereas studies in communities across the country are few.[6,7] Because risk factors that may contribute to increased prevalence of VRE infection include prior exposure to antibiotics,[8,9] we studied HIV-infected patients to determine if their long-term antibiotic therapy (for the prevention and treatment of various opportunistic infections) predisposes them to an increased chance of colonization with VRE. We surmised that rectal intercourse among homosexual males and promiscuous behavior of HIV-infected patients would serve to perpetuate any existing VRE rectal colonization, analogous to the documented spread of VRE via contaminated rectal thermometers.[10]

Materials and Methods

Specimen Collection

Patients were enrolled in the study from the outpatient clinic for HIV-infected patients at the King-Drew Medical Center, Los Angeles. The Medical Center caters to the health care needs of a predominantly minority population of South Central Los Angeles. The study was approved by the Institutional Review Board for the Protection of Human Rights, and informed consent was obtained from all participants. Stool samples were collected using rectal swabs and placed in a holding medium (Stuart's) until processed by the laboratory.

Specimen Processing

All samples were plated onto *1*) bile esculin azide (BEA) agar containing 10 µg/ml vancomycin (Hardy Diagnostics, Santa Maria, CA) and *2*) phenylethyl alcohol (PEA) agar containing 5% sheep's blood (Hardy Diagnostics). Plates were incubated at 35°C and examined after 24 and 48 hours for bacterial growth. All colonies growing on BEA plates (bile esculin–positive or –negative) were gram-stained. Yeast, gram-negative rods, and gram-positive rods (*Lactobacillus* sp.) were discarded. Gram-positive cocci were subcultured onto blood agar and incubated overnight at 35°C. PEA was inoculated by conventional techniques for isolation. Gamma-hemolytic colonies observed on PEA were tested for catalase activity.

Organism Identification and Susceptibility Testing

Gram-positive, catalase-negative cocci were identified, and their sensitivity to vancomycin was determined using a Microscan gram-positive Combo MIC 9 panel. Inocula were prepared by suspending organisms in 0.9% sterile saline to produce turbidity equal to a 0.5 McFarland standard. All panels were incubated for a full 24 hours before being read by the Microscan. Gram-positive, vancomycin-resistant, catalase-negative cocci that were not identified as enterococci by the Microscan

From Charles R. Drew University of Medicine and Science, Martin Luther King Jr.–Charles R. Drew Medical Center, and UCLA School of Medicine, Los Angeles, California.

Reprint requests to Vinod K. Dhawan, MD, Division of Infectious Diseases, Department of Internal Medicine, King-Drew Medical Center, 12021 S. Wilmington Ave, Los Angeles, CA 90059.

ABBREVIATIONS USED IN TEXT
VRE = vancomycin-resistant enterococci

panel were further identified as *Pediococcus* sp. (negative pyrrolidonyl arylamidase [PYR] test and positive leucine arylamidase activity [LAP] test) or *Leuconostoc* sp. (negative PYR and LAP tests) using Bacticard Strep test cards (Remel, Lenexa, KS).[11]

Clinical Data Collection

Clinic records were reviewed for patients' demographic information including age, sex, race, sexual orientation, ongoing or recent (within a month) antibiotic use, and hospitalization within the preceding month.

Results

A total of 89 patients were studied for fecal colonization with VRE (Table 1). They ranged in age from 24 to 62 years, the majority (54 patients) being young adults from 20 to 40 years old. The ethnic background of patients studied, nearly two-thirds African-American and a third Hispanic, mirrors the general racial mix of our patient population. There were 70 men (including 41 homosexual and five bisexual) and 19 women (1 bisexual). Seven men and 2 women declined to reveal their sexual orientation. The patients were on various anti-retroviral treatment regimens which, being unlikely to alter the intestinal microbial colonization, were not specifically recorded. Fifty-three (60%) patients were either on ongoing antibacterial therapy or had received antibiotics in the preceding 1-month period. The antibacterials included trimethoprim/sulfamethoxazole (29 patients), clarithromycin (18), amoxicillin (7), ofloxacin (3), and metronidazole, doxycycline, dicloxacillin, and phalaxin (1 each). Nine patients were receiving more than one of the antibiotics. None of the patients studied had been recently hospitalized.

VRE were not isolated from any of the HIV-infected patients studied. Vancomycin-resistant, gram-positive, catalase-negative organisms were isolated from 5 patients (6%), including *Pediococcus* sp. in 2 and *Leuconostoc* sp. in 3 patients. No distinctive features were noted in those patients with regard to their stage of HIV infection, sexual practices, or antibiotic usage.

Discussion

Enterococci are a part of the normal flora of the human gastrointestinal tract[12] and may also be isolated in 25% of healthy persons from oropharynx, vagina, urethra, and skin.[13] The recovery of enterococci from both the community-acquired and the nosocomially-acquired infections is, therefore, not surprising. Incidence of enterococcal infection has increased in recent years and is currently the second most common nosocomial infection in the United States (after *Escherichia coli*).[14]

TABLE 1. *Demographics of HIV-Infected Patients (total number of patients studied = 89)*

	Number (percent)
Age (years)	
20–40	54 (61)
41–60	34 (38)
>60	1 (1)
Sex	
Men	70 (79)
Women	19 (21)
Race	
Black	61 (69)
Hispanic	25 (28)
White	3 (3)
Sexual orientation	
Heterosexual	33 (37)
Homosexual	41 (46)
Bisexual	6 (7)
Undisclosed	9 (10)
Antibacterial drug use	
Present	53 (60)
Absent	36 (40)

Data are *n* (%).

Increasing resistance of enterococci to vancomycin over the last decade has produced a growing concern over limited treatment options. VRE, first noted in Europe in 1986[15,16] and in the United States in 1988,[17] has rapidly emerged as "the nosocomial pathogen of the 1990s".[18] Nationally, nosocomial infections from VRE have increased from 0.4% in 1989 to 10% in 1995.[18] Intestinal reservoir is of major importance because the carrier status has been correlated with clinical infections.[19] Once acquired, VRE carrier state can last for several months, serving as an important way these organisms spread.[20]

Several risk factors have been associated with the emergence of VRE colonization and infection in hospitals, such as extended hospitalization and prolonged antimicrobial therapy.[8,9] Vancomycin therapy has been frequently reported to be a risk factor for colonization,[21–26] but the risk is not limited to vancomycin; several other antibiotics, such as third-generation cephalosporins,[9,23] fluoroquinolones,[27] aztreonam,[7] metronidazole,[8] clindamycin,[8] and imipenem,[8] have all been shown to predispose to VRE colonization and infection.

In the United States, environmental contamination with VRE is considered rare, although epidemiologic studies of the prevalence of VRE in community settings have been few.[6,7] Coque and associates studied the prevalence of VRE in healthy volunteers and environmental sources in the greater Houston metropolitan area.[6] No healthy volunteer without hospital contact had VRE colonization, and no VRE were isolated from the 44 commercial chickens, 5 farm-raised chickens, 3 turkeys, or 2 chicken farm lagoon slurries. The authors

realized that their findings may not be representative of other parts of the country and suggested the need for further epidemiologic investigations in different settings. In another study, Morris et al. failed to find VRE colonization in stool samples of 16 healthy volunteers.[7] Recently, a Van A *E. faecium* was recovered from dog food.[28]

European studies have documented VRE carrier state in healthy volunteers.[2] In addition, VRE have been recovered from environmental sources such as sewage[29–31] and from frozen poultry.[29,32] The use of the glycopeptide avoparcin in animal feed in Europe has been suggested to be responsible for the emergence of glycopeptide-resistant enterococci, initially in animals and then in humans.[33] Community-acquired infections due to VRE have been reported in Belgium,[2,4] France,[3] and Germany.[5] Thus far, VRE are not extensively disseminated in European hospitals[34,35] as they are in the United States.

Studies of patients attending U.S. outpatient chronic hemodialysis centers have documented a higher prevalence of VRE infection in patients with end-stage renal disease.[36] Our study focused on the risk of colonization with VRE among individuals outside the hospital, and on HIV-infected patients as a sentinel population in whom to detect this risk. HIV-infected patients are frequently treated with antibiotics (trimethoprim/sulfamethoxazole, fluoroquinolones, clarithromycin, azithromycin, rifabutin) for the prevention and treatment of various opportunistic infections. These therapies can potentially alter the normal intestinal flora, resulting in colonization with resistant organisms. Moreover, highly promiscuous behavior of homosexual and bisexual men can conceivably spread rectal organisms (via rectal intercourse) among sex partners. Nosocomial transmission of VRE has been previously documented via contaminated objects such as electronic rectal thermometers.[10]

Our failure to find VRE in the stool samples of HIV-infected patients, combined with the negative findings of other surveys among individuals in the community, suggests that the carriage rate of VRE in U.S. communities is quite low. Conceivably, the screening procedures may have missed VRE present in barely detectable numbers in the feces[2,5] (broth enrichment in antibiotic-free medium has been suggested to improve the yield[5]). Furthermore, nosocomial isolation of VRE from our hospitalized patients is quite sporadic, suggesting a very low prevalence of these organisms in the patient population. Since we did not find VRE colonization in any of our patients, we could not evaluate the possibility of spread of VRE by rectal intercourse among the homosexual males. It remains to be seen if homosexual activity can facilitate the spread of these organisms in communities with a high prevalence of VRE infection.

Acknowledgment

The authors thank Dr. Wilbert Jordan for facilitating patient participation in the study.

REFERENCES

1. Gaynes R, Edwards J. National Nosocomial Infection Surveillance (NNIS) System. Nosocomial vancomycin resistant enterococci (VRE) in the United States, 1989-1995: the first 1000 isolates [abstract]. Infect Control Hosp Epidemiol 1996; 17 (suppl 5 pt 2):18

2. Van der Auwera P, Pensart N, Korten V, Murray BE, Leclercq R. Influence of oral glycopeptides on the fecal flora of human volunteers: selection of highly glycopeptide-resistant enterococci. J Infect Dis 1996; 173:1129–1136

3. Boisivon A, Thibault M, Leclercq R, The Collège de Bactériologie-Virologie-Hygiène des Hôpitaux généraux français. Colonization by vancomycin-resistant enterococci of the intestinal tract of patients in intensive care units from French general hospitals. Clin Microbiol Infect 1997 (in press)

4. Gordts B, Van Landuyt H, Ieven M, Vandamme P, Goossens H. Vancomycin-resistant enterococci colonizing the intestinal tracts of hospitalized patients. J Clin Microbiol 1995; 33:2842–2846

5. Klare I, Heier H, Claus H. *Enterococcus faecium* strains with van A–medicated high-level glycopeptide resistance isolated from animal foodstuffs and fecal samples of humans in the community. Microbial Drug Resistance 1995; 1:265–272

6. Coque TM, Tomayko JF, Ricke SC, Okhyusen PC, Murray BE. Vancomycin-resistant enterococci from nosocomial, community and animal sources in the United States. Antomicrob Agents Chemother 1996; 40:2605–2609

7. Morris JEJ Jr, Shay DK, Hebden JN, McCarter RJ Jr, Perdue BE, Jarvis W, et al. Enterococci resistant to multiple antimicrobial agents, including vancomycin. Establishment of endemnicity in a university medical center. Ann Intern Med 1995; 123:250–259

8. Edmond MB, Ober JF, Weinbaum DL, Pfaller MA, Hwang T, Sanford MD, Wenzel RP. Vancomycin-resistant *Enterococcus faecium* bacteremia: risk factors for infection. Clin Infect Dis 1995; 20:1126–1133

9. Leclercq R, Courvalin P. Resistance to glycopeptides in enterococci. Clin Infect Dis 1997; 24:545–556

10. Livornese LL Jr, Dias S, Samel C, Romanowski B, Taylor S, May P, et al. Hospital-acquired infection with vancomycin-resistant *Enterococcus faecium* transmitted by electronic thermometers. Ann Intern Med 1992; 117:112–116

11. Ruoff KL. *Leuconostoc*, *Pedicoccus*, *Stomatococcus*, and miscellaneous gram-positive that grow aerobically. In: Murray PR, ed. Manual of Clinical Microbiology, 6th ed. Washington, DC, American Society for Microbiology, 1995, p 323

12. Murray BE. The life and times of the Enterococcus. Clin Microbiol Rev 1990; 3:46–65

13. Chenoweth C, Schaberg D. The epidemiology of enterococci. Eur J Clin Microbiol Infect Dis 1990; 9:80–89

14. Schaberg DR, Culvier DH, Gaynes RP. Major trends in the microbial etiology of nosocomial infection. Am J Med 1991; 91 (suppl 3B):72S–75S

15. Uttley AHC, Collins CH, Naidoo J, George RC. Vancomycin-resistant enterococci [letter]. Lancet 1988; i:57–58

16. Leclercq R, Derlot E, Duval J, Courvalin P. Plasmid-mediated resistance to vancomycin and teicoplanin in *Enterococcus faecium*. N Engl J Med 1988; 319:157–161

17. Spera RV Jr, Farber BF. Multidrug-resistant *Enterococcus faecium*: an untreatable nosocomial pathogen. Drugs 1994; 48:678–688

18. Spera RV Jr, Farber BF. Multiply-resistant *Enterococcus faecium*: the nosocomial pathogen of the 1990s. JAMA 1992; 268:2563–2564

19. Wells CL, Juni BA, Cameron SB, Mason KR, Dunn DL, Ferrieri P, Rhame FS. Stool carriage, clinical isolation, and mortality during an outbreak of vancomycin-resistant enterococci in hospitalized medical and/or surgical patients. Clin Infect Dis 1995; 21:45–50

20. Noskin GA, Cooper I, Peterson LR. Vancomycin-resistant *Enterococcus faecium* sepsis following persistent colonization. Arch Intern Med 1995; 155:1445–1447

21. Boyle JF, Soumakis SA, Rendo A, Herrington JA, Gianarkis DG, Thurberg BE, Painter BG. Epidemiologic analysis and genotypic characterization of a nosocomial outbreak of vancomycin-resistant enterococci. J Clin Microbiol 1993; 31:1280–1285

22. Handwerger S, Raucher B, Alstarac D, Monka J, Marchione S, Singh KV, et al. Nosocomial outbreak due to *Enterococcus faecium* highly resistant to vancomycin, penicillin, and gentamicin. Clin Infect Dis 1993; 16:750–755

23. Montecalvo MA, Horowitz H, Gedris C, Carbonaro C, Tenover FC, Issah A, et al. Outbreak of vancomycin-, ampicillin-, and aminoglycoside-resistant *Enterococcus faecium* bacteremia in an adult oncology unit. Antimicrob Agents Chemother 1994; 38:1363–1367

24. Moreno F, Grota P, Crisp C, Magnon K, Melcher GP, Jorgensen JH, Patterson JE. Clinical and molecular epidemiology of vancomycin-resistant *Enterococcus faecium* during its emergence in a city in southern Texas. Clin Infect Dis 1995; 21:1234–1237

25. Linden PK, Pasculle AW, Manez R, Kramer DJ, Fung JJ, Pinna AD, Kusne S. Differences in outcomes for patients with bacteremia due to vancomycin-resistant *Enterococcus faecium* or vancomycin-susceptible *E. faecium*. Clin Infect Dis 1996; 22:663–670

26. Rubin LG, Tucci V, Cercenado E, Eliopoulos G, Isenherg HD. Vancomycin-resistant *Enterococcus faecium* in hospitalized children. Infect Control Hosp Epidemiol 1992; 13:700–705

27. Zervos MJ, Bacon AE 3d, Patterson JE, Schaberg DR, Kauffman CA. Enterococcal superinfection in patients treated with ciprofloxacin. J Antimicrob Chemother 1988; 21:113–115

28. Dunne WM. Watch out where the huskies go. ASM News 1996; 62:283

29. Bates J, Jordens JZ, Griffiths DT. Farm animals as a putative reservoir for vancomycin-resistant enterococcal infection in man. J Antimicrob Chemother 1994; 34:507–514

30. Klare I, Heier H, Claus H, Witte W. Environmental strains of *Enterococcus faecium* with inducible high-level resistance to glycopeptides. FEMS Microbiol Lett 1993; 80:23–29

31. Torres C, Reguera JA, Sanmartin MJ, Perez-Diaz JC, Baquero F. VanA-mediated vancomycin-resistant *Enterococcus* spp. in sewage. J Antimicrob Chemother 1994; 33:553–561

32. Klare I, Heier H, Claus H, Reissbrodt R, Witte W. VanA-mediated high-level glycopeptide resistance in *Enterococcus faecium* from animal husbandry. FEMS Microhiol Lett 1995; 125:165–171

33. van den Boggard AE, Jemsen LB, Stobberingh EE. Vancomycin-resistant enterococci in turkeys and farmers. N Engl J Med 1997; 337:1558–1559

34. Schmit JL, Leclercq R, Scheimherg A, Landauer D. Approche epidemioloique et clinique des enterocoques: resultats d'une enquete. Med Maladies Infect 1994; 24 (suppl):141–148

35. Vandamme P, Vercauteren E, Lammens C, Pensart N, Ieven M, Pot B, et al. Survey of enterococcal susceptihility patterns in Belgium. J Clin Microhiol 1996; 34:2572–2576

36. Tokars JI, Miller ER, Jarvis WR. Vancomycin-resistant enterococci and vancomycin use in outpatient hemodialysis centers [abstract]. 37th Intersci Conf Antimicrob Agents Chemother. Toronto, Ontario, Canada, 1997, p 294

Articles

Dysfunctional Uterine Bleeding

BERTHA H. CHEN; MD, *and* LINDA C. GIUDICE, MD, PhD, *Stanford, California*

Abnormal uterine bleeding is a common, debilitating condition. Dysfunctional uterine bleeding (DUB) is the diagnosis given to women with abnormal uterine bleeding in whom no clear etiology can be identified. DUB has been observed in both ovulatory and anovulatory cycles. Medical treatments include nonsteroidal anti-inflammatory drugs, oral contraceptive pills, progestins, danazol (a synthetic androgen), GnRH agonists, and antifibrinolytic drugs. The drawback to medical therapy, in addition to side effects, is that the benefit lasts only while the patient takes the medication. Surgical options have concentrated mainly on endometrial ablation and hysterectomy, and it is unclear whether one is superior to the other in terms of long-term outcome and patient satisfaction. Newer and less invasive ablation techniques, such as thermal balloon ablation, offer more treatment alternatives.

(Chen BH, Giudice LC. Dysfunctional uterine bleeding. West J Med 1998; 169:280–284)

Menorrhagia and intermenstrual bleeding, respectively, account for 31 and 9 per 1000 consultations of women annually (Morbidity Statistics in General Practice, 1981–1982). Although age of menopause has remained the same over this century, the magnitude of menstrual disorders has increased, likely because of shortened breast-feeding intervals, fewer pregnancies per woman, higher frequency of permanent sterilization, and later age of conception. A woman can expect roughly 400 menstrual cycles during her reproductive lifespan, and it is estimated that up to 20% of women will have excessive menstrual blood loss.[1]

Heavy menstrual bleeding or menorrhagia may occur during pregnancy or may be due to organic disease such as myoma, polyps, infection, carcinoma, or systemic illness. The diagnosis of dysfunctional uterine bleeding (DUB) is given to the group of patients in whom there is no definitive underlying lesion. DUB can occur at any time between menarche and menopause in ovulatory or anovulatory cycles. The latter tends to be more common at puberty and after age 40, times at which irregular ovulation is often encountered.

Abnormal Menstrual Loss

According to the strict definition, menorrhagia is menstrual bleeding longer than 7 days or in an amount exceeding 80 ml from normal secretory endometrium after normal ovulation.[2] Only 40% of women with the complaint of excessive menstrual loss have it confirmed by objective methods, however, and the amount of menstrual blood loss is not proportional to the duration of bleeding or the number of sanitary pads or tampons used during menses.[3] Measurements of hemoglobin extracted from sanitary pads using the alkaline hematin method were obtained by Hallberg et al.,[1] who demonstrated that the mean menstrual blood loss between ages 15 and 50 was 35 ml. The upper limit for diagnosis of menorrhagia was set at 80 ml because two-thirds of women (95th percentile) show evidence of iron-deficiency anemia with that degree of bleeding.[4]

The alkaline hematin method gives an accurate and objective measurement of blood loss, but it is time-consuming and impractical for widespread clinical use. A detailed clinical history, with specific questions designed to investigate the use of sanitary protection and degree of social embarrassment, may be more helpful. Most women with an objective diagnosis of menorrhagia use super or maxi pads, often two at a time, or a super pad with a tampon, and change every 0.5 to 2 hours. The passage of blood clots, flooding, or socially embarrassing bleeding are also reliable indicators of menorrhagia. Fraser[5] asked these types of questions of 50 women complaining of menorrhagia and found that physicians' estimates correlated with objective blood loss measurements overall. A third of the women with objective menorrhagia, however, perceived their menses as light or moderate. Currently, the only available clinical objective evidence of excessive bleeding is laboratory diagnosis of iron-deficiency anemia. Abnormal bleeding that presents as prolonged or decreased bleeding at irregular intervals (usually less than every 21 days) can be verified with a bleeding calendar.

From the Department of Gynecology and Obstetrics/Division of Gynecology, Stanford University, Stanford, California.
Reprint requests to Bertha H. Chen, MD, 300 Pasteur Drive, HH333, Stanford, CA 94305-5317.

ABBREVIATIONS USED IN TEXT

DUB = dysfunctional uterine bleeding
GnRH = gonadotropin-releasing hormone
IUD = intrauterine device
NSAID = nonsteroidal anti-inflammatory drug

Differential Diagnosis

Because DUB is a diagnosis of exclusion, one must rule out organic causes for the abnormal bleeding (after excluding pregnancy). Organic causes can be classified into three major categories: pelvic pathology, systemic diseases, and iatrogenic causes (Table 1); most are in the local pelvic pathology category. Benign pelvic lesions, such as myomas, have been shown to contribute to menorrhagia with varying severity, depending on their location in the uterus.[6] Other benign pathologic conditions include adenomyosis, endometriosis, endometrial or cervical polyps, cervicitis, and severe vaginal infection. These conditions should always be ruled out when a woman presents with abnormal ovulatory bleeding.

Malignant causes of menorrhagia include carcinoma of the reproductive tract and premalignant changes of the endometrium such as hyperplasia. The incidence of endometrial carcinoma in older women is sufficiently high to recommend that all women ages 35 years and above with menorrhagia or abnormal uterine bleeding undergo evaluation of the endometrium. Nearly 40% of premenopausal women with endometrial carcinoma will present with menorrhagia as their only complaint.[7]

Systemic diseases are another important group to consider, including coagulation disorders (thrombocytopathies, Von Willebrand's disease, and leukemia), hypothyroidism, systemic lupus erythematosus, and cirrhosis. Only a small proportion of menorrhagia cases are caused by systemic disease, but severe consequences could result if the diagnosis were missed. Adolescents with coagulation disorders often present with recurrent menorrhagia causing anemia and at times requiring hospitalization.

Iatrogenic etiologies include use of hormone therapy, contraceptive injections and devices, and medications including tranquilizers, antidepressants, anticoagulants, and corticosteroids.

When all the above have been excluded, the diagnosis of dysfunctional uterine bleeding can be given. DUB is a diagnosis that does not apply to menorrhagia only, but also includes excessively prolonged and frequent bleeding (menometrorrhagia). DUB occurs more frequently in anovulatory than ovulatory cycles.

Anovulatory DUB is the end result of unopposed estrogen effects on the endometrium, leading to proliferative, disordered proliferative, hyperplastic, or neoplastic changes. Eventually, desquamation of irregular tissues and focal bleeding occur. Little is known about biochemical disturbances in the local endometrial environment that lead to menorrhagia in anovulatory DUB. Smith et al.[8] demonstrated that arachidonic acid availability is reduced and prostaglandin production is impaired in proliferative endometrium. The imbalance in prostaglandin activity may alter vascular tone, endometrial blood flow, and hemostatic functions. Other factors such as endothelins, endothelium-derived relaxing factor (nitric oxide), and other vasoactive substances may play a role.[9]

TABLE 1.—*Differential Diagnosis of Abnormal Uterine Bleeding*

- I. Pelvic Pathology
  - A. Benign
    - Pregnancy
    - Myoma
    - Adenomyosis
    - Endometriosis
    - Endometrial/cervical polyp
    - Pelvic inflammatory disease
    - Vaginal/cervical infection
  - B. Malignant
    - Carcinoma of the reproductive tract
    - Endometrial hyperplasia
- II. Systemic
  - A. Coagulation disorder
    - Thrombocytopathy
    - Von Willebrand's disease
    - Leukemia
  - B. Hypothyroidism
  - C. Systemic lupus erythematosus
  - D. Cirrhosis
- III. Iatrogenic
  - A. Hormone therapy
  - B. Contraceptive devices and injections
  - C. Medications
    - Tranquilizers
    - Antidepressants
    - Anticoagulants
    - Corticosteroids
- IV. Dysfunctional uterine bleeding

Dysfunctional uterine bleeding associated with ovulatory bleeding is also poorly understood. There is evidence that local factors have a significant influence in the breakdown process. Endometrial lysosomal enzyme activity in ovulatory DUB is increased, leading to the hypothesis that hydrolytic enzymes may participate in the process.[9] There is also evidence that endothelins responsible for local vasoconstriction, migratory leukocytes, and defects in the endometrial repair process may all contribute to abnormal bleeding in ovulatory DUB.

Medical Treatment

Medical therapy for menorrhagia has been poorly researched because of difficulty with objective assessment of menstrual blood loss. Although relatively inexpensive and low in morbidity, side effects are common and benefits cease when the treatment is terminated (Table 2). Long-term side effects and patient compliance should be factors in the decision to treat.

TABLE 2.—*Efficacy and Side Effects of Pharmacotherapy for Management of Menorrhagia*

Drugs	*Efficacy (Reduction in Flow)*	*Side Effects*
NSAIDs	~20–30%	Gastrointestinal
Oral Contraceptives	~50%	Headaches, nausea, edema, weight gain, mood changes, androgenic/hypoestrogenic effects
Progestins	~15%	Headaches, nausea, edema, weight gain, mood changes, androgenic/hypoestrogenic effects
Danazol	~60%	Androgenic
GnRH agonists	100%	Hypoestrogenic/bone loss
Antifibrinolytic Drugs	~80%	Headache, gastrointestinal, vertigo, possible increased thrombotic activity

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Various authors have described disorders of prostanoid synthesis as underlying factors in DUB. Smith et al.[10] reported altered ratio of prostaglandin E2 to F2, and Makarainen and Ylikorkala[11] reported an increased ratio of prostacyclin to thromboxane (prostacyclin causes vasodilation and inhibits platelet aggregation; thromboxane has the opposite effect). It therefore seems reasonable that NSAIDs would be effective treatment, since they reduce prostaglandin levels by inhibiting the cyclooxygenase enzyme when taken during the time of menstruation, and thus tip the balance toward the thromboxane effects. Objective studies measuring menstrual blood loss have shown that NSAIDs can decrease menstrual blood loss by 20–30% in women with menorrhagia.[12]

Oral Contraceptives

The mechanism of action of treatment using oral contraceptives is probably by induction of endometrial atrophy, since their effect is mainly progestational. Reduction of 53% of menstrual blood loss has been reported with oral contraceptive pills containing 50 µg ethinyl estradiol.[13] No controlled study has looked at low-dose oral contraceptive pills in patients with menorrhagia, although the benefit is assumed to be similar.

Progestins

Progestins are frequently used in patients with anovulatory DUB as luteal phase replacement from cycle day 15 to 26. Their role in the treatment of ovulatory dysfunction was not investigated until recent years. In 1990, Cameron et al.[14] noted a reduction of 15% in menstrual blood loss after treatment with norethisterone from cycle day 19 to 26, findings confirmed by Higham and Shaw in 1993.[15] It appears that medicated intrauterine devices (IUDs) may show promise in the treatment of DUB. Levonorgestrel-releasing IUDs have been shown to reduce menstrual blood loss by up to 86% after 3 months of use in women with menorrhagia.[16] IUDs also have the advantage of fewer side effects, since relatively little progestin is absorbed systemically.

Gonadotropin-Releasing Hormone Analogs

A new approach to treatment of DUB is based on the ability of the gonadotropin-releasing hormone (GnRH) antagonists to deplete the pituitary of bioactive gonadotropins and desensitize the pituitary to further GnRH stimulation. The end result is inhibition of further gonadotropin release, suppression of ovarian activity, and hypogonadotrophic hypogonadism. Amenorrhea usually results by 4–6 weeks after initiation of treatment. Postmenopausal symptoms, high cost, and bone demineralization with long-term use are of concern. Combined hormone replacement therapy and GnRH agonists may be a solution.

Danazol

Danazol is a derivative of 17-α-ethinyltestosterone with mild androgenic properties. It works by direct enzymatic inhibition of sex steroid synthesis and competitive inhibition of the binding of sex steroids to androgen and progesterone receptors. It also alters pulsatile gonadotropin release and thus, at higher doses, inhibits ovulation. The end result is endometrial atrophy. The effect of danazol (200 mg/day) has been compared to mefanamic acid (500 mg/day) in a randomized study by Dockeray et al.,[17] who found a 58.9% reduction in menstrual blood loss in the danazol-treated group compared with 22.2% in the NSAID-treated group. Danazol also proved to be more effective than cyclic norethisterone for control of menstrual blood loss.[15] In spite of its proven efficacy, danazol is not frequently used in the United States for menorrhagia because of its androgenic and long-term lipid profile side effects.

Antifibrinolytic Drugs

Antifibrinolytic drugs target the increased fibrinolytic activity in menstrual blood of patients with menorrhagia. Drugs such as tranexamic acid prevent the activation of plasminogen and have been shown to decrease menstrual blood loss by as much as 84%.[13] Reports of intracranial thrombosis with this drug have limited its clinical use.

Surgical Treatment

For many patients, surgical treatment may ultimately be necessary in spite of the effectiveness of medical therapies. Traditionally, dilatation and curettage (D and C) and hysterectomy have been the main forms of treatment for menorrhagia, the former mainly for stabilization of acute episodes of bleeding. The estimated proportion of hysterectomies for DUB annually ranges from 24,750 (4.5% of all hysterectomies per year in the United States)[18] to 292,000 (40%).[19] As with any surgical procedure, cost and morbidity are of concern.

TABLE 3.—*Summary of Randomized Studies Comparing Endometrial Ablation to Hysterectomy*[32]

Reference	Year	Procedure	Number of Patients	Length of Stay (days)	Complications (%)	Patient Satisfaction (%)	Return to Activity (weeks)	Reoperation (%)	Follow-Up (years)
Gannon et al.[27]	1991	Endometrial ablation	25	1	0	NA	2–3	16	1
		hysterectomy	26	7	46	NA	8	—	—
O'Connor et al.[28]	1997	Endometrial ablation	116	1	13	85	3	22	3
		hysterectomy	56	6	45	96	7	—	—
Dwyer et al.[29] and	1993	Endometrial ablation	99	2	4	85	1	23	2
Sculpher[30] et al.	1996	hysterectomy	97	6	47	94	4	—	—
Pinion et al.[31]	1994	Endometrial ablation	105	3	15	78	2–4	16	1
		hysterectomy	99	7	47	89	8–12	—	—

Laparoscopic hysterectomy was introduced to decrease morbidity and cost associated with abdominal hysterectomy, but recent studies have reported greater overall direct cost with laparoscopic hysterectomy compared with abdominal and vaginal hysterectomy because of longer operating times and the use of expensive disposable instruments. The complication rate for abdominal hysterectomy has been reported to be ~9.1%, for vaginal hysterectomy ~7.8%, and for laparoscopic hysterectomy ~8.8%.[20] The majority of complications are due to febrile morbidity and bleeding. Less common, but severe, complications include damage to the urinary tract and gastrointestinal system.

Endometrial Ablation

Endometrial ablation was introduced in the 1980s as an alternative to hysterectomy for DUB. Since then, various types of energy modalities and methods have been used. The ablation is accomplished by hysteroscope using a neodymium:yttrium-aluminum-garnet (Nd:YAG) laser or electrocautery (rollerball and resectoscope). Electrocautery is more commonly used in the clinical setting because of ease of use and lower cost. Other research procedures include the use of radiofrequency energy and cryotherapy for ablation.

Short-term data indicate that endometrial ablation is at least 90% effective in eliminating or reducing bleeding.[21] Surgical complications include uterine perforation, infection, hemorrhage, and fluid overload with pulmonary and cerebral edema. Ablation does not involve the removal of the uterus and thus decreases the recovery and operative time and complications associated with wound healing. Several reports with longer follow-up time, 4 years, have emerged and are finding that up to 34% of women who had an initially successful ablation treatment experience recurrent symptoms requiring additional treatment.[22,23] Other symptoms such as pain can also evolve.[24] Potential long-term complications also include hematometra and occult development of endometrial hyperplasia/carcinoma.[25] Another area of concern is the potential diagnostic difficulty in the evaluation of an ablated uterine cavity; areas of scarring in the cavity may make visualization of potential lesions via hysteroscopy and endometrial biopsy difficult.

Recently, a new method of endometrial ablation has been made available. This technique uses thermal energy for ablation of uterine tissue. A balloon catheter is placed in the uterus through the cervical canal and inflated with 5% dextrose in water. The medium is heated to 87°C while circulating through the balloon during the ablation. The procedure can be done under local anesthesia in the office, and hysteroscopy is not required for insertion. A success rate of 86% after 1 year of treatment has been reported.[26]

Four randomized studies, all from the United Kingdom, have compared hysterectomy to endometrial ablation (Table 3). Overall, ablation was associated with shorter hospital stays, fewer postoperative complications, lower cost, and earlier resumption of activities compared with hysterectomy.[27–31] Because of the relatively small sample size and short follow-up periods, however, it is not clear whether these short-term benefits are sufficient to counteract the disadvantages. A multicenter, randomized study by the Gynecologic Studies Group funded by the Agency of Health Care Policy and Research is investigating these issues further.

Conclusions

Dysfunctional uterine bleeding is a common problem in women of reproductive age, and up to 20% of women affected will seek consultation. Anovulatory DUB, commonly seen at both ends of the reproductive years because of hypothalamic immaturity and changes associated with menopause, is usually treated effectively by replacing the missing component, progesterone, in the luteal phase. The mechanism for ovulatory DUB is less well understood. Medical treatments such as NSAIDs, oral contraceptive pills, progestins, danazol, GnRH agonists, and antifibrinolytic drugs all reduce menstrual flow; however, the benefits are limited to the duration of therapy. Objective measurements of menstrual blood loss continue to be a problem with clinical studies.

Surgical options, other than hysterectomy, have been developed over the past 10 years for treatment of menorrhagia, mainly in the endometrial ablation category. A new form of ablation using thermal energy via an intrauterine balloon appears promising and less

invasive. The main disadvantage of these ablation procedures is potential recurrence of symptoms and missing an occult malignancy, in addition to losing future ability to fully assess the uterine cavity due to scarring. Ongoing studies will help clarify the long-term benefits. Ultimately, good patient selection and long-term follow-up are still the most important factors in success and safety of treatment.

REFERENCES

1. Hallberg L, Hogdahl AM, Nilsson L, Rybo G. Menstrual blood loss: a population study. Acta Obstet Gynecol Scand 1966; 45:320–351

2. American College of Obstetrics and Gynecology. Dysfunctional uterine bleeding. Tech Bull 1982; 66:5

3. Chimbira TH, Anderson ABM, Turnbull AC. Relation between measured menstrual blood loss and patient's subjective assessment of loss, duration of bleeding, number of sanitary towels used, uterine weight and endometrial surface area. Br J Obstet Gynaecol 1980; 87:603–609

4. Cohen BJB, Gibor Y. Anemia and menstrual blood loss. Obstet Gynecol Survey 1980; 35:597–618

5. Fraser IS. Treatment of menorrhagia. In: Dysfunctional Uterine Bleeding and Menorrhagia. Bailliere's Clin Obstet Gynecol London, Bailliere Tindall, 1989; 3:391–402

6. Fraser IS. Hysteroscopy and laparoscopy in women with menorrhagia. Am J Obstet Gynecol 1990; 162:1264–1269

7. Quinn M, Neale BJ, Fortune DW. Endometrial carcinoma in premenopausal women: a clinicopathological study. Gynecol Oncol 1985; 20:298–306

8. Smith SK, Abel MH, Kelley RW, Baird DT. The synthesis of prostaglandins from persistent proliferative endometrium. J Clin Endocrinol Metab 1982; 55:284–289

9. Fraser IS, Hickey M, Song JY. A comparison of mechanisms underlying disturbances of bleeding caused by spontaneous dysfunctional uterine bleeding or hormonal contraception. Human Reprod 1996; 11(suppl 2):165–178

10. Smith SK, Abel MH, Kelly RW, Baird DT. Prostaglandin synthesis in the endometrium of women with ovular dysfunctional uterine bleeding. Br J Obstet Gynaecol 1981; 88:434–442

11. Makarainen L, Ylikorkala O. Primary and myoma-associated menorrhagia: role of prostaglandins and effects of ibuprofen. Br J Obstet Gynaecol 1986; 93:974–978

12. Fraser, IS, Pearse C, Shearman RP, Elliott PM, McIlveer J, Markham R. Efficacy of mefenamic acid in patients with a complaint of menorrhagia. Obstet Gynecol 1981; 58:543–551

13. Nilsson L, Rybo G. Treatment of menorrhagia. Am J Obstet Gynecol 1971; 110:713–720

14. Cameron IT, Haining RH, Lumsden MA, Thomas VR, Smith SK. The effects of mefenamic acid and norethisterone on measured menstrual blood loss. Obstet Gynecol 1990; 76:85–88

15. Higham JM, Shaw RW. A placebo controlled study to compare danazol (200 mg), a regimen of decreasing doses of danazol, and norethindrone in the treatment of objectively proven menorrhagia. Am J Obstet Gynecol 1993; 169:1134–1139

16. Andersson JK, Rybo G. Levonorgestrel-releasing intrauterine device in the treatment of menorrhagia. Br J Obstet Gynaecol 1990; 97:690–694

17. Dockeray CJ, Sheppard BL, Bonnar J. Comparison between mefenamic acid and danazol in the treatment of established menorrhagia. Br J Obstet Gynaecol 1989; 96:840–844

18. Wilcox LS, Koonin LM, Pokras R, Strauss LT, Xia Z, Peterson HB. Hysterectomy in the United States, 1988–1990. Obstet Gynecol 1994; 83:549–555

19. Brooks PG, Clouse J, Morris LS. Hysterectomy vs. resectoscopic endometrial ablation for the control of abnormal uterine bleeding. A cost-comparative study. J Reprod Med 1994; 39:755–760

20. Weber AM, Lee JC. Use of alternative techniques of hysterectomy in Ohio, 1988–1994. N Engl J Med 1996; 335:483–489

21. Brill AI. What is the role of hysteroscopy in the management of abnormal uterine bleeding? Clin Obstet Gynecol 1995; 38:319–345

22. Unger JB, Meeks GR. Hysterectomy after endometrial ablation. Am J Obstet Gynecol 1996; 175:1432–1436

23. Chullapram T, Song JY, Fraser IS. Medium-term follow-up of women with menorrhagia treated by rollerball endometrial ablation. Obstet Gynecol 1996; 88:71–76

24. Magos AL, Baumann R, Lockwood GM, Turnbull AC. Experience with the first 250 endometrial resections for menorrhagia. Lancet 1991; 337:1074–1078

25. Margolis MT, Thoen LD, Boike GM, Mercer U, Keith LG. Asymptomatic endometrial carcinoma after endometrial ablation. Inst J Gynaecol Obstet 1995; 51:255–258

26. Vilos GA, Fortin CA, Sanders B, Pendley L, Stabinsky SA. Clinical trial of the uterine thermal balloon for treatment of menorrhagia. J Am Assoc Gynecol Laparosc 1997; 4:559–565

27. Gannon MJ, Holt EM, Fairbank J, Mitzgerald M, Milne MA, Crystal MA, Greenhalf JO. A randomised trial comparing endometrial resection and abdominal hysterectomy for the treatment of menorrhagia. BMJ 1991; 303:1362–1364

28. O'Connor H, Broadbert JAM, Magos AL, McPherson K. Medical Research Council randomised trial of endometrial resection versus hysterectomy in management of menorrhagia. Lancet 1997; 349:897–901

29. Dwyer N, Hutton J, Stirrat GM. Randomised controlled trial comparing endometrial resection with abdominal hysterectomy for surgical treatment of menorrhagia. Br J Obstet Gynaecol 1993; 100:237–243

30. Sculpher MJ, Dwyer N, Byford S, Stirrat GM. Randomized trial comparing hysterectomy and transcervical endometrial resection: effect on health related quality of life and costs two years after surgery. Br J Obstet Gynaecol 1996; 103:142–149

31. Pinion SB, Parkin DE, Abramovich DR, Naji A, Alexander DA, Russell IT, Kitchener HC. Randomised trial of hysterectomy, endometrial laser ablation, and transcervical endometrial resection for dysfunctional uterine bleeding. BMJ 1994; 309:979–983

32. STOP-DUB Coordinator Center. Surgical Treatments Outcomes Project for Dysfunctional Uterine Bleeding. 1997; pp 1–5

Epitomes

Important Advances in Clinical Medicine

Radiology

Nancy Ellerbroek, MD, and John McGahan, MD, Section Editors

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in radiology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, as to both scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in radiology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Radiology of the California Medical Association, and the summaries were prepared under the direction of Drs. Nancy Ellerbroek and John McGhan and the Panel.

Intensity Modulated Radiation Therapy

THE GOAL OF RADIATION therapy treatment planning is to deliver a maximal dose to the tumor-bearing region, while minimizing the dose to sensitive normal tissues surrounding the tumor. Currently this task is usually performed by shaping the incident treatment fields to the projection of the tumor using simple customized blocks. The radiation beams are of uniform intensity across the field, or modified by simple devices such as tungsten wedges.

A new approach, intensity modulated radiation therapy (IMRT), uses radiation beams in which the beam intensity or energy deposition per unit time (fluence) varies by several orders of magnitude across the face of each beam. It is a cross-firing process that has been compared to computerized tomographic (CT) scanning. CT delivers a uniform radiation exposure to the patient and the non-uniform attenuation of the beam is measured to reconstruct the cross-sectional image. IMRT delivers a non-uniform radiation exposure from multiple angles to create a uniform dose distribution within the tumor.

Knowledge of normal tissue resistance to the effect of radiation is necessary for IMRT planning. When the tumor is not separated from surrounding normal organs at risk (e.g., when the target wraps around organs at risk), adding modulation to geometric shaping of the beam may be the best way to adequately treat the tumor while sparing the normal tissue. IMRT joins proton or heavy-particle radiation therapy as ways to deliver the concave dose distributions that will allow for organ-sparing for irregularly shaped tumors and contiguous normal tissues. The beam is segmented into a series of tiny "beamlets," and the fluence of each beamlet is made proportional to the tumor thickness as assessed from the angle that the beamlet traverses the tumor. Where the tumor is thickest, the intensity is at its greatest; where it is thinnest, the intensity is least. By cross-firing the target with beams of varying intensity, a relatively uniform dose distribution can be built up across the volume of the tumor.

IMRT development has depended upon the development of separate but related technologies: (1) fast and inexpensive digital computation for treatment planning, (2) new optimization algorithms to calculate the numbers of beams, their non-uniform fluence, and the beam positions, (3) the new imaging technologies including CT, MR, digital angiography, and PET for tumor localization, (4) patient and tumor immobilization, (5) verification of treatment delivery (both for accuracy of optimization and fidelity to plan specification), and (6) computer networking to orchestrate all of the above technologies.

There are two candidate IMRT delivery systems. The multi-leaf collimator (MLC) consists of a set of narrow tungsten leaves, projecting 1-cm wide at the center of rotation of the linear accelerator gantry. These leaves can be individually positioned under computer control to shadow portions of the uniform beam during treatment, producing the beamlets required for IMRT. A second system uses a narrow "mini-MLC" that is added to the standard linear accelerator. The beam is turned on and off by driving the mini-MLC leaves to either an open or a shut position. Treatment is delivered to narrow, 2–4-cm slices of the tumor in a rotational fashion. At each rotation, the patient is moved inward, positioning an untreated portion of the tumor for treatment.

Each approach has its advantages. The "standard" MLC can treat the whole patient at once, but currently requires a retrofit of only the most modern accelerators and costs approximately $400,000. The computer planning software for this device is at an early stage in development, and the entire treatment "chain"—from planning to accelerator and from collimator control code

to verification—is still in development at a few academic centers. The "mini" MLC can be added to any accelerator, indeed can even be retrofit to a cobalt treatment machine. It is about 1/4 the price of the standard device. The mini-MLC system has been commercialized and is in clinical use at approximately 20 centers in the United States. Since only a portion of the treatment can be delivered at any one time, however, the treatment may take as long as 30 minutes instead of the 5–10 minutes of "beam on" time. Also, exact registration of the slices (the stepwise movement of the patient inward with respect to the treatment beam after each rotation) is critical to avoid overdose or underdose where the slices abut.

Early clinical results have been published for head and neck cancers, for CNS malignancy, and for prostate cancer. Doses in the range of 8600 cGy have been achieved for prostate cancer without increased acute rectal and bladder toxicity, compared with conventional treatment to doses of 6600–7000 cGy. Patients with central aerodigestive-tract malignancy and involved neck nodes have been locally controlled with less xerostomia due to the ability to spare the salivary glands from significant radiation dose. Tumors wrapped around the optic nerve or spinal cord have been treated with therapeutic doses without any degradation of vision or motor function. The Radiation Therapy Oncology Group is currently planning a phase III trial of this modality vs. conventional treatment. Subsequent to this trial the radiation oncology community may anticipate that technology transfer could occur rapidly, so that the approach will become available to benefit appropriately selected patients with potentially curable local tumors.

CHRISTOPHER M. ROSE, MD, FACR
Burbank, California

REFERENCES

Carol MP. A system for planning and rotational delivery of intensity-modulated fields. Special issue on optimization of the three-dimensional dose delivery and tomotherapy. Int J Imag Syst Technol 1995; 6:56–61

Purdy JA. Intensity-modulated radiation therapy. Int J Radiat Oncol Biol Phys 1996; 35:845–846

Ling CC, Burman C, Chui CS et al. Conformal radiation treatment of prostate cancer using inversely-planned intensity modulated photon beams produced with dynamic multileaf collimation. Int J Radiat Oncol Biol Phys 1996; 35: 721–730

The Future of Teleradiology in Medicine

TELERADIOLOGY ALLOWS THE VIEWING of diagnostic imaging studies at a site remote from the imaging location and has historically been used for on-call coverage, particularly of CT and ultrasound. Now, technology and the forces of medicine have combined to develop two new possibilities. One potentially enables any clinician to review, at any location, imaging studies (and reports) of patients under his or her care. The other allows imaging specialists to perform remote primary interpretation.

Initially, most teleradiology systems were quite crude and slow, and often captured image data with only moderate resolution and accuracy. Today, these systems are increasingly connected or integrated to a Picture Archiving and Communication System (PACS), using the Digital Imaging Communication in Medicine (DICOM) standard of the American College of Radiology.

Currently, a combination of increased computing power, including high speed and abundant memory at very reasonable cost, enables the remote display of a more accurate and detailed representation of the original image. Display technology has also improved to the degree that these systems have the capability to view conventional radiographs, in addition to CT, ultrasound, and MR, provided the images are captured at appropriate resolution. Communication technology allows movement of images at greater speed via fast modems, ISDN, and dedicated communication links inside and outside of hospitals. In addition, advances in the area of image compression allow the packing of image data more tightly, which further enhances transmission speed. Compression methods known as *wavelets* appear to allow high compression with no perceptible loss of diagnostic information.

Security for teleradiology is an area that is being addressed, partly in response to new government regulations for patient privacy protection. Teleradiology systems are being used increasingly for remote interpretation, particularly for CT and MR, raising issues of credentialing, licensing, and traditional relationships between referring clinicians and local radiologists. Image transmission and the viewing process are somewhat slower than a dedicated in-hospital PACS, unless similar workstations are used. Projection radiology, i.e. bone and chest, is technically more challenging.

Most recently the World Wide Web has provided exciting new software solutions to the problem of moving image data. It is in use today at many academic centers. Clinicians can expect to have access to patients' images at any location once this technology is more widely available. Ideally, advanced teleradiology will enable improved diagnostic imaging for underserved populations.

DAVID E. AVRIN, MD, PHD
KATHERINE P. ANDRIOLE, PHD
San Francisco, California

REFERENCE

Dure-Smith P, Fymat AL. Teleradiology: will it transform the practice of radiology? Radiology 1997; 203:49A–50A

New Methods of Treatment for Cerebral Aneurysms

THERE IS NOW almost a decade of accumulated clinical experience with the Guglielmi Detachable Coil (GDC) in the treatment of cerebral aneurysms. This represents a major new option in the "minimally invasive treatment" methods now available to patients with cerebrovascular disease and stroke. The basic GDC design consists of a helical platinum coil attached to a stainless steel delivery wire. Under x-ray guidance, the soft platinum coil is positioned within the aneurysm lumen via a microcatheter navigated to the aneurysm neck. Once a satis-

factory configuration is attained, the coil is detached from the delivery wire by electrolysis. The objective is to pack the aneurysm with a sufficient number of coils to induce endosaccular thrombosis and occlusion, thus preventing arterial inflow. This technique obviates the need for a surgical craniotomy. Approximately 27,000 patients have undergone this treatment.

The most satisfying technical results are seen in smaller aneurysms (<12-mm diameter) with narrow necks. Wide-necked aneurysms remain technically challenging because of the proclivity of coil loops to cross the broad neck and herniate into the parent arterial lumen. Fusiform aneurysms also remain a challenge because occlusion of the aneurysm lumen usually results in simultaneous blockage of the parent artery.

In addition to factors related to aneurysm morphology, the feasibility of endovascular aneurysm treatment also relates to the aneurysm site. Middle cerebral artery aneurysms are usually more difficult to treat because of more complex anatomical arrangements encountered in this location. For treatment of posterior circulation aneurysms, however, endovascular techniques may offer advantages over surgical clipping because of difficult surgical access and the risk of injury to small arterial perforator vessels and neural structures. Other potential advantages of the endovascular route over surgery are that brain retraction is avoided (especially relevant in acute aneurysms where the brain may be swollen and edematous), and the ability to stage procedures in medically compromised patients with large or complex acute aneurysms.

A longer-term problem associated with the use of GDC is the phenomenon of coil compaction. Over time the endosaccular coil conglomerate may compact, resulting in partial recanalization of the aneurysm, usually at the neck. For this reason, follow-up angiography is necessary. The likelihood of coil compaction may correlate to the density and completeness of the original coil pack, the size of the aneurysm and aneurysm neck, the presence of aneurysm thrombus, and the position of the aneurysm. End-artery locations such as terminal carotid or basilar tip aneurysms may be prone to coil compaction because the direction of the arterial inflow vector is perpendicular to the aneurysm neck, producing a so- called water-hammer effect against the coils.

The largest published series examining the efficacy of the GDC system in treatment of acute subarachnoid hemorrhage is a North American multi-center prospective trial in which 403 patients were enrolled. All of these patients were excluded from aneurysm surgery because of technical difficulty, poor medical condition, or other reasons and therefore represent a high-risk group. The proportion of posterior circulation aneurysms within this cohort was 57%. The overall reported rates of morbidity and mortality were 9% and 6% respectively. These figures compare favorably with the natural history of untreated ruptured aneurysms. The data suggest that GDC embolization in subarachnoid hemorrhage may be less effective in giant aneurysms (>2.5-cm. diameter) and may not improve clinical outcomes in those patients with pre-existent poor clinical status. A European multicenter prospective randomized controlled trial comparing surgery to endovascular treatment of ruptured aneurysms is currently in progress. Rebleeding rates following endovascular coiling remain to be defined. The preliminary data are encouraging, however, indicating an overall rebleeding rate of 0.5% or less per annum. A recent prospective study of clinical outcomes (average of 3.5 years follow-up) found 86% of 61 patients treated with GDC for acute subarachnoid hemorrhage had an excellent or good outcome.

Valid comparisons of morbidity and mortality with surgical clipping in acute subarachnoid hemorrhage, particularly with respect to anterior cerebral circulation aneurysms (and especially anterior communicating artery aneurysms which overall are the most common) are difficult to make using the current data. The results of prospective randomized controlled trials are awaited. Endovascular technology, however, continues to evolve rapidly, as does clinical expertise with these techniques, forecasting further improvement in healing aneurysms using the endovascular route.

CONSTANTINE C. PHATOUROS, MBBS, FRACR
RANDALL T. HIGASHIDA, MD
VAN V. HALBACH, MD
San Francisco, California

REFERENCES

Vinuela F, Duckwiler G, Mawad M. Guglielmi detachable coil embolization of acute intracranial aneurysm: perioperative anatomical and clinical outcome in 403 patients. J Neurosurg 1997; 86:475–482

Byrne JV, Sohn MJ, Lim W, Bacon F, Shrimpton J, Molyneux AJ. Late rebleeding after coil embolization. Proceedings of The Symposium Neuroradiologicum XVI 1998; 11:229–230 (239S, Abstract)

McDougall CG, Halbach VV, Dowd CF, Higashida RT, Larsen DW, Hieshima GB. Endovascular treatment of basilar tip aneurysms using electolytically detachable coils. J Neurosurg 1996; 84:393–399

Malisch TW, Guglielmi G, Vinuela F, Duckwiler G, Gobin P, Martin NA, Frazee JG. Intracranial aneurysms treated with the Guglielmi detachable coil: midterm clinical results in a consecutive series of 100 patients. J Neurosurg 1997; 87:176–183

Extracranial Carotid Stenosis: Ultrasound, MRI, Angiography

In experienced hands, with proper instrumentation, vascular ultrasound is the screening study of choice for extracranial carotid artery disease because it is accurate, non-invasive, and the least costly of the three main options. This technique uses bilateral morphologic images to assess the extent of plaque and tortuosity, and to determine whether there is a high carotid bifurcation. Another essential component is an evaluation of flow dynamics using color Doppler, and spectral analysis in the internal carotid artery, the external carotid artery, the vertebral artery, and the proximal, mid, and distal portions of the common carotid artery.

To assure quality of operator and instrumentation, the sonogram should be done in an accredited laboratory under the supervision of an experienced registered vascular technologist. Laboratory accreditation is obtained through either the Intersociety Commission for the Accreditation of Vascular Laboratories or the American College of Radiology Vascular Ultrasound Accreditation Program.

If the carotid stenosis is greater than 70% and there is no suggestion of other complicating factors, some surgeons will proceed directly to carotid endarterectomy, depending upon whether the sonogram is technically adequate. Others prefer to corroborate the sonogram before surgery with magnetic resonance angiography (MRA), particularly if questions exist. A confirmatory study is important if flow is damped, suggesting bilateral carotid ostial disease (or cardiac disease) out of the field of view of ultrasound that can be visualized by MRA. Other indications for MRA confirmation are detection by sonography of elevated carotid velocities, which may result from shunted flow from a significant lesion of the opposite carotid artery; suspected internal carotid occlusion; or highly resistant flow in a normal-appearing carotid artery, suggesting dissection out of the sonographic field of view.

MRA is also indicated in evaluating for random lesions and to differentiate between vessel occlusion versus "angiographic string sign" suspected on ultrasound.

Carotid catheter angiography has historically been the standard to which the other studies are compared. The examination has inherent risks, albeit low, but with potential for morbidity and even mortality. Recent studies suggest that when compared with the actual carotid specimen removed intact at the time of endarterectomy, extra-cranial carotid artery disease is significantly underdiagnosed by catheter angiography. Angiography, however, remains an integral part of the workup in that small group of patients in which there is a discrepancy between the ultrasound and magnetic resonance angiographic studies.

GRETCHEN A. W. GOODING, MD
San Francisco, California

REFERENCES

Wain RA, Lyon RT, Veith FJ, Berdejo GL, Yuan JG, Suggs WD, Ohki T, Sanchez LA. Accuracy of duplex ultrasound in evaluating carotid artery anatomy before endarterectomy. J Vasc Surg 1998; 27:235–242; discussion 242–4

Saloner D, Reilly LM, Anderson CM, Diaz M, Gooding GAW, Rapp JH. Evaluation of disease of the carotid bifurcation using magnetic resonance imaging. J d'Echographie et de Med Ultrasons.1996; 17:348–356

Pan XM, Saloner D, Reilly LM, et al. Assessment of carotid artery stenosis by ultrasonography, conventional angiography, and magnetic resonance angiography: Correlation with ex vivo measurement of plaque stenosis. J Vasc Surg 1995; 21:82–89

Ultrasound versus CT in Evaluating Blunt Abdominal Trauma

INJURIES FROM BLUNT trauma are primarily the result of motor vehicle accidents, and continue to increase along with motor vehicle use in the United States and worldwide. Rapid diagnosis and early surgical intervention decrease morbidity and mortality from these injuries. To detect intraabdominal injury from blunt trauma, emergency physicians and trauma surgeons have several options: physical examination, laboratory tests, observation, diagnostic peritoneal lavage, ultrasound, and computerized tomography (CT).

Physical examination and laboratory tests are not accurate in detecting intraabdominal injury. The presence of abdominal tenderness to palpation is neither sensitive nor specific for intraabdominal injury, and is unreliable in obtunded or unconscious patients. Patients with multiple distracting injuries will also have unreliable abdomen exams. Laboratory tests indicating fall in hematocrit greater than 5% or abnormal liver function are questionable. Admission to the hospital and observation may be useful in the diagnosis of subtle or occult intraabdominal injury—including bowel and mesentery injuries—which are notoriously difficult to detect with imaging studies. Admission and observation may also be appropriate for selected spleen and liver injuries for which non-operative management has been chosen. In the era of managed care and shrinking medical resources, however, the practice of admission for observation is declining.

Diagnostic peritoneal lavage remains the most sensitive method for detecting intraabdominal injury, and is indicated for obtunded or unconscious patients. The majority of blunt trauma patients treated by emergency physicians are stable and awake, however, and diagnostic peritoneal lavage is inappropriate for this subgroup. It is also an invasive procedure requiring a substantial amount of time and effort, making it difficult for the busy emergency physician to perform alone. It is more appropriate for a trauma center with a dedicated trauma team. A positive diagnostic peritoneal lavage provides no information about the site of bleeding and does not identify isolated retroperitoneal injuries. Because of the extreme sensitivity of this technique, a greater number of non-therapeutic laparotomies have been reported from the use of diagnostic peritoneal lavage as an initial screen for intraabdominal injury.

Ultrasound has many qualities which make it an attractive initial screening test for intraabdominal injury. It is portable, rapid, noninvasive, and relatively inexpensive, and it involves no parenteral or oral radiocontrast exposure. It can be performed during the trauma resuscitation. Serial ultrasound examinations are easily obtained.

Reported sensitivities for detection of intraabdominal injury range from 63% to 100%. There are variations in study design and method of scanning, however. The amount of intraperitoneal fluid required for ultrasound detection remains unclear, but is widely regarded as approximately 500 mL. Although some studies utilize a single scan of the hepatorenal interface (Morison's pouch), which is considered positive if a stripe of fluid is seen, the single view has largely been abandoned, and a more comprehensive sonographic examination has evolved.

Focused abdominal sonography in trauma (FAST) is now the most commonly used method worldwide in the detection of intraabdominal injury. The FAST scan can be completed in less than 5 minutes and involves up to 6 views: (1) subxiphoid to detect pericardial effusion; (2) right upper quadrant view to assess Morison's pouch, diaphragm, liver, and kidney; (3) left upper quadrant to assess the splenorenal interface, spleen, diaphragm, and kidney; (4 and 5) right and left flank to assess kidneys; and (6) longitudinal pelvis to look for free fluid adjacent to the bladder. The development of the FAST technique

was based on observations of the location of intraperitoneal fluid collections in the supine patient, which were the pelvic cul-de-sac, Morison's pouch, and pericolic gutters. Recent studies comparing the single-view scan to the FAST scan noted significant improvement in sensitivity, specificity, and accuracy with a slight increase in total examination time.

Studies assessing the FAST technique for detecting hemoperitoneum report sensitivities from 63% to 98% and specificities above 90%. Localization of specific organ injuries by ultrasound is less successful, with sensitivities ranging from 44% to 73% for all combined organ injuries. Solid organ injuries, such as spleen and liver, are more accurately identified with ultrasound than bowel and mesentery injuries. Ultrasound has better sensitivity for detecting parenchymal spleen injuries than liver injuries. A negative ultrasound examination cannot completely rule out the possibility of intraabdominal injury. Up to 26% of patients with intraabdominal injury from blunt trauma may have no hemoperitoneum identified on ultrasound or CT.

Ultrasound represents a snapshot in time. Obtaining a repeat ultrasound after a period of time or significant deterioration in clinical status may detect these occult injuries. Further studies are required to answer this question. Some potential disadvantages of ultrasound include variable operator training level and experience, and imaging limitations from obesity, luminal bowel gas, subcutaneous emphysema, and ascites.

CT scanning has been proven to be the ideal imaging study for the detection of intraabdominal injury. Unlike diagnostic peritoneal lavage and ultrasound, it enables localization and grading of specific organ injuries, which are important in determining operative versus nonoperative management. CT also may identify pneumothoraces, fractures of the spine and pelvis, and vascular injuries which may not have been apparent on initial plain radiographs. Multiple studies have demonstrated CT to have sensitivities and specificities consistently above 90%. Yet another advantage is helical CT, which has significantly shorter scanning time. CT, while excellent at detecting solid-organ intraabdominal injury, is less accurate for bowel and mesentery injuries.

Disadvantages of CT include the necessity of intravenous and oral contrast, which expose the patient to the risk of adverse drug reaction. The patient must be transported from the emergency department, so CT is not appropriate for unstable patients. Pediatric patients often require parenteral sedation to successfully complete the CT exam, which requires constant monitoring and carries the risk of airway compromise. CT nevertheless remains the optimal imaging study in the detection of intraabdominal injury.

As emergency physicians and surgeons become more familiar with ultrasound, it will be increasingly utilized as the initial screening tool for detection of blunt intraabdominal injury. The impact of this usage will be decreasing reliance on diagnostic peritoneal lavage. CT will probably be utilized more frequently for initial detection of intraabdominal injury; localization and grading of intraabdominal injury for positive ultrasound exams; and confirmation of negative ultrasound exams. CT will also be used to determine which patients require admission and which may be safely discharged home from the emergency department.

JOHN R. RICHARDS, MD
Sacramento, California

REFERENCES

Pearl WS, Todd KH. Ultrasonography for the initial evaluation of blunt abdominal trauma: a review of prospective trials. Ann Emerg Med 1996; 27:353–361

Sherbourne CD, Shanmuganathan K, Mirvis SE, Chiu WC, Rodriguez A. Visceral injury without hemoperitoneum: a limitation of screening abdominal sonography for trauma. Emerg Rad 1997; 4:349–354

Porter RS, Nester BA, Dalsey WC, et al. Use of ultrasound to determine need for laparotomy in trauma patients. Ann Emerg Med 1997; 29:323–330

Richards JR, Derlet RW. Computed tomography for blunt abdominal trauma in the ED: a prospective study. Am J Emerg Med 1998; 16:338–342

Katz S, Lazar L, Rathaus V, Erez I. Can ultrasonography replace computed tomography in the initial assessment of children with blunt abdominal trauma? J Ped Surg 1996; 31:649–651

Imaging Renal and Ureteral Stones

PATIENTS WITH RENAL or ureteral stones usually seek medical attention for renal colic. Passage of a uretal stone is often accompanied by some degree of obstruction of the ipsilateral ureter and/or renal collecting system. Intravenous urography (IVP) has long been the gold standard in evaluating these patients. It may confirm that a suspected calculus demonstrated on a plain radiograph lies within the ureter and determine the presence and degree of obstruction. IVP can also detect obstruction secondary to non-radiopaque stones. Intravenous urograms, however, can be time-consuming and may require delayed imaging up to 24 hours after the initiation of the study. In addition, IVP requires the use of iodinated contrast material, to which a small but significant number of patients are allergic. Iodinated contrast can also be nephrotoxic, especially in patients who have renal insufficiency.

Recent studies have demonstrated the superiority of non-contrast helical computed tomography (CT) over IVP in evaluating patients presenting with acute flank pain. The advantages of CT include its rapid acquisition times; the fact that it is performed without the use of iodinated contrast or patient preparation; and its high sensitivity and specificity in detecting renal and ureteric stones and ureteral obstruction. Traditionally, the cost of an abdominal pelvic CT scan is greater than that of an IVP, but varies from one institution to another. However, since the CT study used for imaging renal and ureteral stones does not require oral or intravenous contrast, some institutions charge for a limited CT scan and have lowered the cost of the CT study to equal or compare favorably to the cost of an IVP. CT may also diagnose other disease entities unrelated to the genitourinary tract, which may be responsible for a patient's flank pain.

Non-contrast helical CT has been shown to be quite sensitive and specific in the detection of renal and ureteric stones. A recent study found that CT detects

obstructing ureteric calculi with a sensitivity of 98%, a specificity of 100% and positive and negative predictive values of 100% and 97% respectively. In a direct comparison of non-contrast helical CT, ultrasound and IVP in the detection of ureteral stones, CT was found to be the superior of the three modalities. The sensitivity and specificity of CT was 94% and 97% respectivly with an accuracy of 95%, whereas IVP had a sensitivity and specificity of 52% and 94% respectivly and an accuracy of only 66%. Ultrasound was the inferior of the three modalities and had a sensitivity and specificity of 19% and 97%, and aan accuracy of 45%. Stones may be visualized within the renal pelvis and intrarenal collecting system, in the ureter, at the ureterovesicular junction, and in the bladder. Obstruction due to a ureteral stone may result in a number of associated findings on non-contrast helical CT. These include enlargement of the affected kidney, perinephric stranding or edema—which may be visualized as linear areas of increased density within the fat surrounding the kidney—and dilatation of the intrarenal collecting system and ureter to the level of the intraureteral stone. The presence of unilateral ureteral dilatation and perinephric stranding has been shown to have a high positive predictive value for the presence of stone disease (99%), whereas the lack of these two findings has been shown to have a high negative predictive value in excluding stone disease (95%). Once a ureteral stone has been identified, the level of the obstruction can easily be determined. The size of the stone can be accurately measured using helical CT. Furthermore, nearly all stones are visualized regardless of stone composition, since even uric acid stones are greater in density than soft tissue and therefore easily detected by CT. The axial images obtained during a non-contrast helical CT of the abdomen can be reformatted to create coronal images similar to those obtained during an intravenous urogram. These can be used to enhance communication between the radiologist and the referring clinician.

Occasionally, phleboliths within the pelvis along the course of the ureter may be confused with a ureteral stone. A rim of soft tissue around a suspected calculus has a 31-to-1 odds ratio of representing a ureteral stone as opposed to a phlebolith. Reformatted coronal images may also be useful in demonstrating the relationship of a pelvic calcification to the ureter.

Ultrasonography has also been used to evaluate patients presenting with acute flank pain. When ultrasonography is utilized, the detection of hydronephrosis and/or hydroureter is used to determine whether or not obstruction is present. Ultrasound, however, may fail to detect hydronephrosis within the first 24 hours. Ultrasound is also operator-dependent, and quite often visualization of the ureter and site of obstruction can be limited. In a comparison of non-contrast helical CT to the combination of plain film and ultrasound, non-contrast CT was found to be superior in detecting ureteral calculi and perinephric fluid.

In many cases, acute flank pain may be caused by disease entities unrelated to the genitourinary tract. In these cases, one would expect an intravenous urogram to be normal. More recent studies have demonstrated that non-contrast helical CT is quite useful in determining other disease entities which may account for the patient's flank pain. These include diseases of the bowel, such as diverticulitis or appendicitis, or other disease entities such as pancreatitis, adnexal masses, or leaking abdominal aortic aneurysm.

The radiation doses received by the patients undergoing non-contrast helical CT can be similar to that of intravenous urography (depending on the number of radiographs obtained for the IVP). Non-contrast helical CT, unlike intravenous urography, does not give information about renal function. It has been suggested by some authors that the degree of obstruction and renal dysfunction may be proportional to the amount of perinephric stranding and fluid present on non-contrast helical CT. In many institutions, since non-contrast helical CT does not require oral or intravenous contrast material or patient preparation, the cost of the helical CT is reduced to compare favorably with that of the intravenous urogram.

In summary, non-contrast CT has been shown to be superior to intravenous urography in the detection of renal and ureteric stones; in determining the degree and level of obstruction; and in offering alternative diagnoses to account for the patient's flank pain if no stone is present. Non-contrast helical CT can be performed quickly and without patient preparation. Since intravenous contrast is not used, there is no risk of allergic reaction or nephrotoxicity. Non-contrast helical CT may be considered the modality of choice in evaluating patients presenting with acute flank pain.

C. DARRYL JONES, MD
Sacramento, California

REFERENCES

Smith RC, Rosenfield AT, Choe KA, et al. Acute flank pain: comparison of non-contrast-enhanced CT and intravenous urography. Radiology 1995; 194:789–794

Sommer FG, Jeffrey RB Jr, Rubin GD, et al. Detection of ureteral calculi in patients with suspected renal colic: value of reformatted noncontrast helical CT. AJR 1995; 165:509–513

Fielding JR, Steele G, Fox LA, Heller H, Loughlin KR. Spiral computerized tomography in the evaluation of acute flank pain: a replacement for excretory urography. J Urol 1997; 157:2071–2073

Smith RC, Dalrymple NC, Neitlich J. Noncontrast helical CT in the evaluation of acute flank pain. Abdom Imaging 1998; 23:10–16

Yilmaz S, Sindel T, Arslan G, et al. Renal colic: comparison of spiral CT, US and IVU in the detection of ureteral calculi. Eur Radiol 1998; 8:212–217

Management of Locally Advanced Prostate Cancer: New Definitions and Strategies

Until the mid 1990s, the term "locally advanced prostate cancer" referred to a stage of prostate cancer determined by digital rectal exam to have palpable evidence of cancer penetrating the capsule of the prostate. This definition was challenging from its inception and with time it has become even less useful. Prostate cancer at this stage, also called stage "C" or "T3" disease, was

associated with a 30% to 50% likelihood of lymph node involvement, and most radiation oncologists and many urologists considered such patients unsuitable for a radial prostatectomy. Such patients were usually treated with radiotherapy alone, and it was widely believed that the local control rate approached 70%.

Recent studies have demonstrated that the clinical extent of disease determined by palpation does not provide the most critical information for determining long-term prognosis. The availability of the serum marker prostate specific antigen (PSA) in the late 1980s is largely responsible for recognition of the shortcomings of the traditional definition of locally advanced prostate cancer. With the availability of the PSA, it became clear that many patients who would previously have been declared "cured" did in fact have active disease.

Based on contemporary criteria for what really should be considered locally advanced disease, locally advanced prostate cancer is quite common. These criteria include cancers with a high likelihood of not being organ-confined at the time of surgery, and cancers with a high rate of local failure with standard-dose radiotherapy. Until very recently, most surgical studies demonstrated that nearly half of all patients with clinical stages below T3 who were treated with radical prostatectomy were found to have cancer extension beyond the capsule (pathological T3 disease).

Studies evaluating the local status of the disease using biopsies demonstrated that local failure was the rule and not the exception for patients with bulky tumors. Because of sampling errors (false-negative biopsies), the true incidence of local failure is probably underestimated considerably. A rising serum PSA appears to be the most sensitive way to define disease status, thus PSA has become the gold standard for treatment failure.

Despite the value of the PSA as a tumor marker, it appears that tumor grade and stage are better predictors of prostate cancer mortality. The most widely accepted (and respected) grading system was described by Gleason. Total Gleason-pattern score—a sum of the two most common histologic patterns—correlates with pathologic stage and survival and cancer-specific survival. When matched for pre-treatment PSA, patients evaluated by Gleason score compared with T stage appeared to do equally well (or poorly) when treated with either radiotherapy or surgery. The independent thresholds for a poor outcome appear to include a pre-treatment PSA >10 ng/ml, Gleason score >7 and clinical stage >T3. Patients possessing 2 or more of these factors should be considered to have locally advanced disease. Unfortunately, sampling errors and errors arising from inaccurate readings by pathologists have been reported to compromise the accuracy of Gleason-score readings in community hospitals.

In the mid to late 1980s, because of high local failure rates for high-risk patients treated with conventional doses of radiotherapy, computer-based treatment planning focused on the development of "three-dimensional conformal radiotherapy" (3DCRT). This technology allowed a reduction in the dose of radiation delivered to surrounding normal tissues while higher doses were delivered to the prostate. Several retrospective studies have now demonstrated both a reduction in the acute toxicity and an improvement in PSA responses with the use of higher doses in some patients. Despite these encouraging impressions, however, only prospective randomized trials will prove that higher doses are safe and more effective at achieving local control as well as freedom from disease and improved chances for overall survival.

Experimental and clinical data suggest that there may be synergistic interactions between androgen suppressive hormonal therapy and radiation. Recent prospective randomized trials have shown that the use of neoadjuvant (before and during) hormonal therapy is associated with an improvement in local control and disease-free survival. Other studies demonstrated a progressive reduction in the incidence of positive biopsies when hormonal therapy is added to radiotherapy. Two more recent studies provide evidence of a survival benefit when adjuvant hormonal therapy is added to radiation.

Based on the best available data, Gleason score >7 (tumor grade), and high serum PSA (> 10 ng/ml) as well as T stage should be used to define high-risk or locally advanced prostate cancer. The benefits of higher doses of radiation need to be confirmed in prospective randomized trials, but improved CT-based imaging (3D conformal radiotherapy) is probably here to stay. Patients with several poor risk factors, including clinical stage >T3, Gleason score >7 and/or PSA >10 ng/ml, should probably be managed with androgen ablation lasting 1, 2 or even 3 years or longer in addition to radiotherapy.

MACK ROACH III, MD
San Francisco, California

REFERENCES

Roach M. The role of PSA in the radiotherapy of prostate cancer. Oncology 1996; 10:1143–1153

Zietman A, Nakfoor B, Prince E, Gerweck L. The effects of androgen deprivation and radiation therapy on an androgen-sensitive murine tumor: an in vitro and in vivo study. Cancer J Sci Am 1997; 3:31–36

Laverdiere J, Gomez JL, Cusan L, et al. Beneficial effect of combination therapy administered prior and following external beam radiation therapy in localized prostate cancer. In J Radiat Oncol Bio Phys 1997; 37:247–252

Bolla M, Gonzalez D, Warde P, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. N Engl J Med 1997; 337:295–300

Pilepich MV, Caplan R, Byhardt RW, et al. Phase III trial of androgen suppression using goserlin in unfavorable-prognosis carcinoma of the prostate treated with definitive radiotherapy: report of Radiation Oncology Group Protocol 85–31. J Clin Oncol 1997; 15:1013–1021

ADVISORY PANEL TO THE SECTION ON RADIOLOGY

ANTON N. HASSO, MD
Advisory Panel Chair
CMA Council on Scientific Affairs Representative
University of California, Irvine

FRED B. TOMLINSON, MD
CMA Section Assistant Secretary
Santa Cruz

CHARLES GOODING, MD
Immediate Past Panel Chair
San Francisco

DAVID B. HINSHAW, JR., MD
Loma Linda University

GARY GLAZER, MD
Stanford University

JAMES BRUNBERG, MD
University of California, Davis

RICHARD J. STECKEL, MD
University of California, Los Angeles

GEORGE R. LEOPOLD, MD
University of California, San Diego

RONALD L. ARENSON, MD
University of California, San Francisco

JAMES HALLS, MD
University of Southern California

KATHRYN DUKE
CMA Staff
San Francisco

LESLIE BIRNBAUM
CMA Staff
San Francisco

RAYMOND T. CUMMINS, MD
Special Society Representative
Larkspur

DAVID LARSON, MD
Special Society Representative
San Francisco

KENNITH CHIN, MD
Special Society Representative
Northridge

NANCY ELLERBROEK, MD
Special Society Representative
Mission Hills

ROBERT ACHERMANN
Invited Guest
Sacramento

JOSEPH BRUGMAN, MD
Member at Large
Santa Ana

ERIK OLSON, MD
Member at Large
San Luis Obispo

MURRAY A. REICHER, MD
Member at Large
San Diego

Y. JOE KWON, MD
Member at Large
Apple Valley

JAMES F. LONGO, MD
Member at Large
Templeton

TOM WEISENBURGER, MD
Member at Large
Santa Barbara

Alerts, Notices, and Case Reports

Illness Associated With Eating Seaweed, Hawaii, 1994

KATHERINE L.E. MARSHALL, DVM, MS
Atlanta, Georgia
RICHARD L. VOGT, MD
Honolulu, Hawaii

SEVEN OF 13 PEOPLE (54%) at a Labor Day picnic on the island of Hawaii in 1994 became ill with gastrointestinal symptoms within 15 to 90 minutes of eating lunch. We conducted a retrospective cohort study to determine what food served at the picnic was related to the illness. All 7 people who ate the seaweed preparation became ill. Two of them ate less than one serving (defined as one serving spoon) of seaweed and experienced only a burning sensation in the mouth and throat; the 5 who ate one or more servings experienced more serious gastrointestinal illness. The seaweed was identified as *Gracilaria coronopifolia*, a species usually considered to be nontoxic. Water sample analysis from the harvest area indicated an increased level of enterococci in the water during the month of harvest, although the increase was not above acceptable standards. Mouse and guinea pig assays revealed that the seaweed contained debromoaplysiatoxin and aplysiatoxin, two toxins that possibly came from the blue-green algae found on the seaweed. This is the first reported outbreak of seaweed poisoning in Hawaii; in Guam, a previously undescribed toxin in *Gracilaria tsudai* caused the death of 3 people in 1991. Data from both incidents suggest that seaweeds usually considered nontoxic may occasionally produce poisons associated with illness in humans.

In the Pacific Islands, seaweed (algae) is often served as a side dish at meals, and it is an important component in the diet of many who reside in the Pacific Rim. The seaweed is usually obtained by harvesting it at beaches, gathering it in near-shore waters, or purchasing it at local markets. It is served either raw or cooked and is often eaten with salt or mixed with spices such as garlic, chili pepper, soy sauce, and ginger. Although illness after consumption of seaweed has been reported in other parts of the Pacific (Guam,[1] California,[2] and Japan[3]), seaweed toxicity has never been reported to the Hawaii Department of Health.

On Sept. 9, 1994, a 60-year-old woman on the island of Maui telephoned the local health department to report a burning sensation in her mouth and throat that began 15 minutes after she had tasted a seaweed or *ogo* preparation. The woman had washed the seaweed, boiled it in water for 1–2 minutes, and then mixed it with vinegar, sugar, soy sauce, and sliced cucumbers. Six hours after tasting the dish, she became ill with a headache and generalized myalgia. When examined by a physician the next day, she had a headache and a sore throat and mouth. A throat culture was negative for group A streptococcus. No other household members had tasted the seaweed, and samples were unavailable because the woman had disposed of the seaweed after becoming ill. She had received the seaweed on Sept. 1, 1994, from her son's friend, who had gathered the seaweed at a site in a bay on a northeast-facing windward shore in Maui County.

Six days earlier, on Sept. 3, 1994, a 49-year-old woman on the island of Hawaii had received seaweed obtained from the same source. When later contacted by the local district health department, she reported a burning sensation in her mouth and throat that lasted about 4 hours after tasting the preparation she had made from the seaweed. The woman's 50-year-old husband had also tasted the preparation and reported a similar burning sensation. At the time, both had attributed the sensation to chili peppers.

The seaweed was refrigerated until it was prepared on September 4. The woman cleaned it; boiled it for 3–4 minutes; rinsed it; mixed it with codfish, vinegar, onions, shoyu, chili peppers, and tomatoes; and served the preparation at a Labor Day picnic the following day. The local health department contacted those who had attended the picnic and found that 7 of the 13 attendees had gastrointestinal illness characterized by nausea and diarrhea soon after eating at the picnic. This report summarizes the epidemiologic investigation of those illnesses and discusses several other seaweed-associated outbreaks in recent years.

Methods

The Hawaii Department of Health conducted a retrospective cohort study of all picnic attendees to determine whether illness was caused by eating the seaweed served at the picnic. A survey questionnaire was administered by telephone; picnic attendees were asked which foods they had consumed, if and when onset of illness had occurred, and symptoms of illness. A case was defined as illness in a picnic attendee who, within 2 hours of eating food items from the picnic, had either a burning sensation in the mouth or throat or two or more of the following symptoms: vomiting, diarrhea, nausea, and lethargy. Food-specific illness rates were calculated using Epi-Info 6.01.

Both the seaweed served at the picnic and another sample obtained from the same harvest site were examined at the University of Hawaii for species identification and toxicity studies. The algae were rinsed well and extracted with acetone. The toxicity of the crude extract was checked by intraperitoneal injection into mice and observation of the mice for symptoms of toxicity. High-performance liquid

(Marshall KLE, Vogt RL. Illness associated with eating seaweed, Hawaii, 1994. West J Med 1998; 169:293–295)

From the Epidemic Intelligence Service State Branch (Dr. Marshall), Division of Applied Public Health Training, Centers for Disease Control and Prevention, Atlanta, Georgia, and the Communicable Disease Division (Dr. Vogt), Department of Health, Honolulu, Hawaii.

Reprint requests to Dr. Paul Effler, State Epidemiologist, Communicable Disease Division, Department of Health, 1250 Punchbowl Ave, Honolulu, HI 96813.

TABLE 1. *Bacteriologic water sampling data in Waiehu, Maui, July–Decmber 1994*

Month	Rainfall (past 24 h) North Point	Rainfall (past 24 h) South Point	Enterococci (#/100 mL) North Point	Enterococci (#/100 mL) South Point
July	No	No	1	1
August	No	No	1	1
September	No	No	4	50
October	Yes	Yes	1	1
November	—*	—*	1	1
December	No	No	1	1

Sampling areas were at stream mouths at the northern (north point) and southern (south point) most points of Waiehu Bay.
*Data unavailable; no samples.

chromatography was used to isolate the exact compound that caused the mice to exhibit the most extreme signs of toxicity. Bacterial organisms on the surface and within the algae were identified microscopically. The bacteria were cultured using 2% NaCl heart infusion agar (DIFCO). Each culture was then extracted, and the extracts were subjected to the mouse toxicity test.[4]

Results

Eight adults and 5 children attended the picnic. Seven (54%) of the 13 attendees became ill within 15–90 minutes of eating the meal, all adults (5 men and 2 women). Of those, 5 reported diarrhea, 5 nausea, 3 vomiting, and 4 a burning sensation. Gastrointestinal symptoms lasted a mean of 22 hours. None of those who fell ill sought medical treatment.

Menu items for the picnic included poi, two types of fish (mamo and awe), beef stew, the seaweed preparation, salmon salad, steak, rice, tuna salad, chips, crackers, beer, soda, and water. Only the 7 who had eaten the seaweed preparation became ill (RR undefined, $P < 0.05$). Of 8 people who ate the salmon salad, the only other food item besides seaweed that was significantly associated with illness, 7 became ill (RR undefined). The seaweed, however, was the only food item that had been eaten by all the ill persons and had not been eaten by those who remained well. Two (29%) of the 7 ate less than one serving (defined as one serving spoon) of seaweed and experienced only a burning sensation in the mouth and throat, whereas the 5 who ate one or more servings had gastrointestinal illness as well.

The implicated seaweed had been harvested from a bay into which two fresh water streams flow at the northern and southern points; in addition, storm drain discharge from the city flows into the stream at the southern point of the bay, and the tides transport tree branches and other debris into the bay. The Hawaii Department of Health's State Wastewater Management Division, Clean Water Branch, collects water samples from this area on a monthly basis and measures rainfall during the 24-hour period before sample collection. The samples are tested for enterococci levels, and any levels <70 colonies/100 ml are considered acceptable by Hawaii Administrative Rules.[5]

The Hawaii Department of Health records of water samples tested during July through December 1994 indicated no unacceptably elevated levels of enterococci (Table 1). Enterococci levels in all those months but one were 1 colony/100 mL; in September, the samples collected from stream mouths at the northern and southern points of the bay (about 1.5 miles apart) were 4 and 50 colonies/100 ml, respectively. According to the Hawaii Department of Health, the current usually flows from south to north, and the bay is most affected by the outflow at the southern end of the bay. No sewage spills, pesticide contamination, or other potential pollutants were reported in the area in the period of time before the seaweed was harvested.

The seaweed was identified as *Gracilaria coronopifolia* with blue-green algae attached and interwoven among the stems of seaweed. Colonies of two different species of *Pseudomonas* and *Vibrio* grew on culture media. Mice injected with extracts from the bacteria exhibited no signs of toxicity other than transient weakness. Extracts from the seaweed caused symptoms of toxicity in the mice; such symptoms ranged from diarrhea at low doses to death within 15 minutes after injection of the most toxic isolate. Two toxic compounds, identified as debromoaplysiatoxin and aplysiatoxin, were isolated using high-performance liquid chromatography.[4]

Discussion

Results of the epidemiologic study implicating seaweed as the source of illness were supported by a dose-effect relationship: those who had eaten only a taste of the seaweed had less severe symptoms than those who had eaten one or more servings.

Laboratory findings of slightly increased levels of enterococci in the seawater at the time the seaweed had been harvested indicated potential microbiologic contamination of the water, even though the levels were within the acceptable water quality standards established by the Hawaii Department of Health. Enterococci testing of water samples does not differentiate between human or animal fecal enterococci and nonpathogenic soil enterococci, and no other causative biologic agents were found in the water. Bacterial organisms were found on and in the algae, but extracts from the bacteria did not cause a toxic reaction when injected into mice. Additional laboratory studies isolated two toxins from the seaweed mix, debromoaplysiatoxin and aplysiatoxin; those toxins caused similar illness in mice and killed them at higher doses.

Blue-green algae was found on the *G. coronopifolia*. Debromoaplysiatoxin and aplysiatoxin are usually found in blue-green algae, specifically the *Lyngbya majuscula* in Hawaii. Although freshwater cyanobacteria have been associated with outbreaks of illness, this is the first gastrointestinal outbreak known to be associated with debromoaplysiatoxin and aplysiatoxin in marine blue-green algae.[6,7] Aplysiatoxin and debromoaplysiatoxin can cause skin irritation characterized by redness, blisters, and a burning or itching sensation of the skin[8,9]; both have been implicated in occurrences of chemical "swimmer's itch" on

various north shore beaches of Oahu. Both are also known to be potent tumor promoters in two-stage carcinogenesis in mouse skin.[10] The potential of these two toxins as tumor promoters in humans is unknown; but their noxious effects are a public health concern. Swimmers and seaweed on leeward shores of the Hawaiian islands rarely come in contact with blue-green algae because trade winds usually transport the algae away from the shore. Slightly elevated enterococci levels in seawater might serve as a signal for a potential health threat of harvesting seaweed for consumption.

Environmental stresses on the seaweed possibly allowed for colonization of the blue-green algae. Previous studies have demonstrated that stress from over-harvesting might cause seaweed to produce toxins as a method of protection and that environmental changes and increased pollution promote colonization of toxin-producing bacteria.[11] Although unlikely in this case, other studies have suggested that some species of seaweed may become toxic at the end of their reproductive cycle, and therefore exhibit a seasonal variation in toxin production.[12]

Although this was the first reported case of seaweed-induced illness in Hawaii, several cases have been reported in the Pacific Rim.[3,13] In 1991, 13 people became ill eating seaweed (*Gracilaria tsudai*) harvested in Guam[1]; 3 died. In addition to gastrointestinal illness, they experienced fever, wheezing, muscle fasciculations, and hypotension. In 1992, according to a press report, 3 people became ill, one of whom was hospitalized, after eating seaweed (*Grasilariopsis lemanaeformis*) picked on the beach of Half Moon Bay in California.[2] In 1993, 2 people became ill, 1 of whom later died, after eating *Gracilaria verrucosa* seaweed in Japan.[3] In the cases in Guam and California, the implicated seaweed was not previously known to be toxic. In the two cases that occurred in Japan, the seaweed was not examined adequately and no toxin was identified. Whether the dearth of reported seaweed-associated illness reflects failure to report illness or infrequent occurrence is unclear.

Since the incident in Hawaii, physicians were alerted to the potential for seaweed-induced toxicity and were requested to report cases to the Hawaii Department of Health. Seaweed has been collected from the same harvest site for toxin surveillance. Until further information regarding seaweed toxicity is known, those who harvest seaweed for consumption should be aware that any seaweed harvested from Hawaiian waters is potentially toxic. Those who experience a burning sensation after eating a seaweed preparation should notify the Hawaii Department of Health.

Although the species of blue-green algae was not identified in this outbreak, *Lyngbya majuscula*, which possibly contains debromoaplysiatoxin and aplysiatoxin and can grow epiphytically on certain edible seaweeds,[8] has been identified in Hawaii.[9] The Hawaii Department of Health recommends that seaweed to which blue-green algae—specifically *Lyngbya* species—is attached should not be eaten. Boiling the seaweed did not inactivate the toxin in the two incidents on Maui and Hawaii. Because the consumption of seaweed is common among many ethnic groups who reside in the Pacific area, additional research is necessary to determine the etiology and extent of seaweed-associated illnesses and to characterize such illnesses.

Acknowledgments

We are indebted to the following persons for their support in reviewing this article and collecting data: Laura Fehrs, MD, Roland Asakura, Mark Hanne, Chester Wakida, Skippy Hau, and Herbert Matsubayashi. We are indebted to Dr. Y. Hokama and Dr. H. Nagai at the University of Hawaii for their laboratory assistance.

REFERENCES

1. Haddock R. Guam seaweed poisoning: food histories. Micronesica 1993; 26:35–38

2. Snyder B. Seaweed suspect in poisoning of Livermore family. Oakland Tribune 1992; Nov 2:1

3. Noguchi T, Matsui T, Miyazawa K, Asakawa M, Iijima N, Shida Y. Poisoning by the red alga 'Ogonori' (*Gracilaria verrucosa*) on the Nojima Coast, Yokohama, Kanagawa Prefecture, Japan. Toxicon 1994; 32:1533–1538

4. Nagai H, Yasumoto T, Hokama Y. Aplysiatoxin and debromoaplysiatoxin as the causative agents of a red alga *Gracilaria coronopifolia* poisoning in Hawaii. Toxicon 1996; 37:753–761

5. Hawaii Administrative Rules (HAR), chapters 11–54, "Water Quality Standards"

6. Huang P, Weber J, Sosin D, et al. The first reported outbreak of diarrheal illness associated with Cyclospora in the United States. Ann Intern Med 1995; 123:409–414

7. Elder G, Hunter P, Codd G. Hazardous freshwater cyanobacteria (blue green algae). Lancet 1993; 341:1519–1520

8. Moore RE. Toxins from marine blue-green algae, The Water Environment; Algal Toxins and Health. New York, NY: Plenum Press, 1981, pp 15–23

9. Codd GA, Poon GK. Cyanobacterial toxins, Biochemistry of the Algae and Cyanobacteria. Oxford: Clarendon Press, 1988, pp 283–296

10. Fujiki H, Ikegami K, Hakii H, et al. A blue-green alga from Okinawa contains aplysiatoxins, the third class of tumor promoters. Jpn J Cancer Res 1985; 76:257–259

11. Meyer KD, Paul V. Intraplant variation in secondary metabolite concentration in three species of Caulerpa (Chlorophyta:Caulerpales) and its effects on herbivorous fishes. Mar Ecol Prog Ser 1992; 82:249–257

12. Yasumoto T. Guam seaweed poisoning: biochemistry of the *Grasilaria* toxin. Micronesica 1993; 26:53–57

13. Fusetani N, Hashimoto K. Prostaglandin E_2, a candidate for causative agent of 'Ogonori' poisoning. Bull Japanese Soc Sci Fisheries 1984; 50:456–469

Sphenoid Pneumoceles Cause Episodic Pressure-Related Blindness

MATTHEW M. HANASONO, MD
ALEXANDER M. NORBASH, MD
KIMBERLY SHEPARD, MD
DAVID J. TERRIS, MD
Stanford, California

THOUGH ETIOLOGIES VARY, transient visual loss in adults is most commonly caused by vascular insufficiency secondary

(Hanasono MM, Norbash AM, Shepard K, Terris DJ. Sphenoid pneumoceles cause episodic pressure-related blindness. West J Med 1998; 169:295–299)

From the Division of Otolaryngology/Head and Neck Surgery (Drs Hanasono, Shepard, and Terris) and Department of Radiology (Dr Norbash), Stanford University Medical Center, Stanford, California

This paper was presented at the Triological Society Western Section Meeting in Tucson, Arizona in January 1997

Reprint requests to David J. Terris, MD, Edwards Building, R135, Stanford University Medical Center, Stanford, California 94305-5328.

to atherosclerotic microemboli or vasospasm of ophthalmic supplying arteries. Rarely, transient visual loss has been associated with disease of the sphenoid sinus, which is adjacent to the optic nerve.[1,2,3] Such cases result from increased pressure within the sphenoid sinus transmitted to the optic canal through a defect in the bony sinus wall. The following case report presents an unusual case of a sphenoid sinus pneumocele which manifested with visual disturbances at high altitudes due to increased air pressure in the sphenoid sinus which was transmitted to the optic nerve in the absence of infection within the optic canal.

Case Report

A 35-year-old avid snow skier with a six-month history of visual disturbances in his left eye reported that on car trips to the Sierra Mountains in Lake Tahoe, California, he would notice visual dysfunction in his left eye that began precisely at an elevation of 5,000 feet, progressing from "seeing stars" and "loss of contrast" to complete left eye blindness. These episodes typically lasted 15 to 20 minutes. This same sequence of visual loss was noted during multiple plane flights, usually beginning 20 minutes after takeoff and also lasting for 15 to 20 minutes. Each episode was accompanied by a left retroorbital headache. He was seen by an otolaryngologist who ascribed the episodes to sinusitis and prescribed methylprednisolone for one day preceding travel as well as Entex (phenylpropanolamine and guaifenesin) and acetaminophen one hour prior to travel. The headaches and visual disturbances continued despite this treatment. The patient found that placing his head between his knees caused the visual disturbances to resolve faster, often within five minutes.

A comprehensive ocular exam by an ophthalmologist and a neuro-ophthalmologist was unremarkable. One month after the onset of his symptoms, while traveling by plane in Europe, the patient developed the usual visual changes accompanied by a left-sided headache and was diagnosed with a retinal hole with operculum during an examination at an eye clinic. This hole was repaired with a laser, but his visual changes and headaches continued to occur during high altitude travel. Computed tomography (CT) and magnetic resonance imaging (MRI) scans that subsequently were obtained demonstrated left sphenoid sinusitis (see Radiologic Findings). The patient was treated with doxycycline and methylprednisolone. He was kept on azithromycin prophylactically, but this failed to prevent the visual disturbances. A neurologist was consulted who made a diagnosis of ocular migraine and prescribed verapamil prior to flying. The visual disturbances continued despite the patient taking increasing doses of verapamil. The patient was then evaluated at the Division of Otolaryngology/Head and Neck Surgery at Stanford University Medical Center. A review of both imaging studies revealed protrusion of the left optic nerve into the superolateral sphenoid sinus.

The patient's past medical history included a three-year history of left-sided headache, morning nasal congestion that was worse on the left, and recurrent nosebleed from the left nostril for many years. He used no medications other than those described above. He was a nonsmoker and reported drinking one glass of wine with dinner each night.

A physical examination showed that, though the patient's nasal septum was deviated to the left, he had no other remarkable physical findings relevant to the head and neck. The patient had normal ocular exam including full visual fields and normal visual acuity.

A translabial, transseptal sphenoidotomy and septoplasty were performed with wide enlargement of the sphenoid ostium and removal of the sphenoidal septum. A transseptal approach was chosen over a transnasal endoscopic approach because of the greater exposure it afforded. Intraoperatively, protrusion of the left optic nerve was apparent within the superolateral wall of the left sphenoid sinus by endoscopy. There was no fluid within the sinus at the time of exploration. Mucosal tissue from the right and left sphenoid sinuses were submitted for pathologic examination. Both specimens were histologically normal. Bacterial cultures from the left sphenoid sinus mucosa grew peptostreptococci species. The patient recovered without complications and has had no further visual dysfunction or retroorbital headaches after several high altitude travel challenges. He remains free of symptoms 18 months after surgery.

Radiologic Findings

Direct coronal CT examinations of the paranasal sinuses were obtained. Coronal sequences consisted of 3 mm thick sections obtained at 4 mm intervals. The coronal CT images demonstrate soft tissue fullness in the roof of the left sphenoid sinus (Figure 1). The bony covering appears to be intact but attenuated on the 3 mm thick section using a standard soft tissue algorithm at a bone window.

MRI sequences included T1 weighted unenhanced sagittal, dual echo T2 weighted unenhanced axial, T1 weighted unenhanced and enhanced axial and coronal sequences. Additional thin-section sagittal and coronal enhanced sequences were obtained, centered on the sphenoid sinus. The MRI study demonstrates nonenhancing layering dependent fluid in the left sphenoid sinus on the enhanced T1 weighted axial sequence (Figure 2). The conventional unenhanced coronal and enhanced thin-section coronal sequences show that there is soft tissue fullness in the roof of the left sphenoid sinus that is nonenhancing, and, therefore, most likely represents the posterior layered fluid that was shown on the axial sequence and has assumed the most dependent portion of the sinus (Figure 3). Hyperintensification of the layering on T2 weighted images, corresponding with presumed fluid or mucosal thickening, was also seen. Additionally, these sequences show that there is no perceptible bony separation either from the medial inferior aspect of the left optic tract or from the medial wall of the cavernous carotid artery, thereby suggesting dehiscence.

Discussion

Pneumoceles of the sphenoid sinus in which air pressure within the sphenoid sinus compresses the optic

Figure 1.—Coronal standard algorithm bone window computed tomography (CT) demonstrates fullness in the roof of the left sphenoid sinus. Although the bony covering appears to be intact on this 3 mm thick section, the superolateral wall of the left sphenoid sinus was dehiscent on endoscopy.

Figure 2.— Enhanced axial magnetic resonance (MR) study demonstrates nonenhancing layering fluid in the left sphenoid sinus. A concha bullosa involves the right middle turbinate. A nasal septal deformity is also seen.

nerve through a defect in the bony sinus wall causing transient visual loss have been reported on three occasions (Table 1).[1,2,3] As in the previous case, these lesions were symptomatic during ascent in aircraft. Wide sinusotomy and, in one case, the removal of a nasal polyp at the sinus ostium resulted in improvement or eradication of the symptoms.

The visual changes in the case previously presented were the result of a relative increase in pressure on an optic nerve that projected into the superolateral sphenoid sinus. The relative increase in pressure within the sinus was caused by a decrease in atmospheric pressure with ascent to higher altitudes combined with the occlusion of a poorly patent sphenoid sinus ostium preventing pressure equalization. The patient's altitude-induced visual changes were fully relieved by enlarging the sphenoid ostium, allowing decompression, drainage of the sinus, and pressure equalization.

The patient's vision changed while driving in the mountains at an altitude of approximately 5,000 feet as

TABLE 1.—*Overview of Reported Cases of Sphenoid Sinus Pneumoceles*

Report	*Age*	*Sex*	*Symptom Presentation*	*Duration*	*Findings*	*Surgery*	*Outcome*
Sugita et al (1977)	26	M	Bilateral blindness	7 y	Enlarged sinus, wall defects	Transmaxillary sphenoidotomy	No further episodes; improved vision
Som et al (1983)	48	M	Left blurred vision to blindness	2 y	Enlarged sinus, very thin or dehiscent sinus wall	Transnasal sphenoidotomy	Cure
Bell et al (1995)	41	M	Left visual field loss to blindness	1 y	Enlarged left sinus, suspected wall defects	Endoscopic ethmoidotomy, sphenoidotomy	Cure
Hanasono et al (1998)	35	M	Left visual disturbance to blindness	1 y	Enlarged left sinus, suspected wall defects	Transseptal sphenoidotomy, septoplasty	Cure

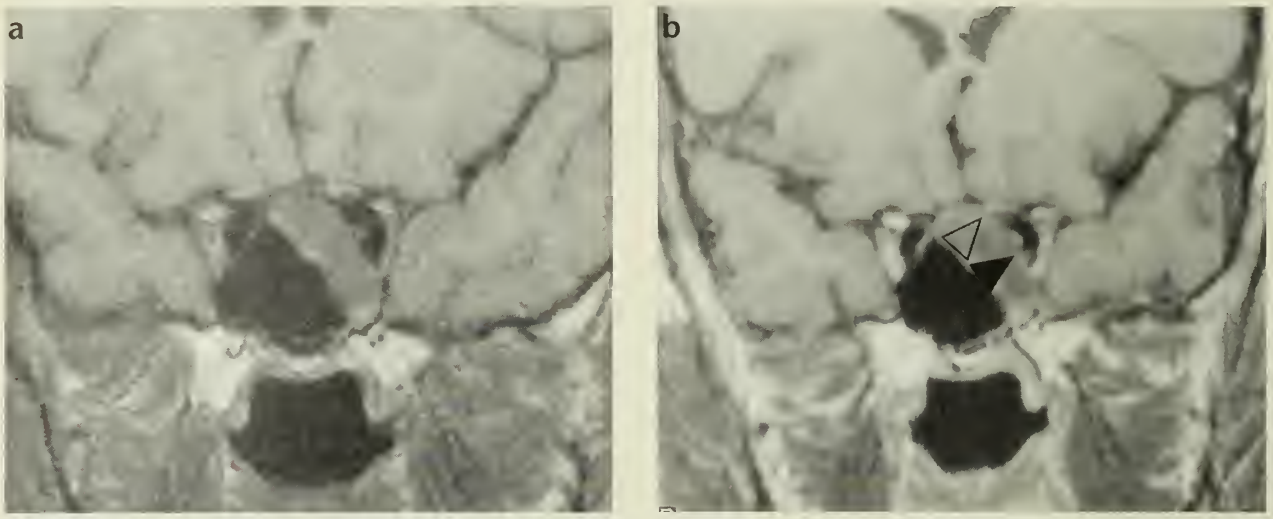


Figure 3.—The conventional unenhanced coronal (a) and enhanced thin-section coronal (b) images show nonenhancing soft tissue fullness in the roof of the left sphenoid sinus. There is no perceptible bony separation either from the medial inferior aspect of the left optic tract (△), or from the medial cavernous carotid artery (▲). There is no significant contrast enhancement of the abnormal sphenoid opacity.

well as during commercial air travel about 20 minutes after takeoff. Most commercial airplanes fly between 31,000 to 41,000 feet in the air and reach their maximum cruise height within 17 to 20 minutes of takeoff. Airlines typically maintain their cabin pressure at 7.8 to 8.65 psi during flight. Since the pressure at 8,000 feet of elevation is around 7.8 psi, airline cabin pressure roughly corresponds to the pressure at which our patient experienced his symptoms while driving in the mountains. The retinal hole discovered by another physician most likely was an incidental finding as his symptoms failed to resolve even after treatment was administered.

Although the sphenoid wall appeared to be intact on CT, the MRI findings as well as direct visualization by endoscopy during surgery on the patient suggest that the bony sinus wall was dehiscent, allowing the transmission of pressure from the sphenoid sinus cavity to the optic nerve. Typically, studies obtained to detail thin or small bony structures, such as orbital floors and temporal bones, are performed as bone algorithms, and these are then displayed as bone windows. In this particular example, had thinner 1 to 1.5 mm sections been performed as a bone algorithm, the lateral dehiscence of the sphenoid sinus may very well have been seen adjacent to the left optic tract. This relationship is very well demonstrated on the high resolution coronal MRI study (Figure 3).

Alternately, pressure may have been transmitted to the optic nerve through a very thin bony wall separating the sphenoid sinus cavity from the optic canal which protruded into the sphenoid sinus. In a study of 150 CT scans of patients without sphenoid disease, 8% were found to have protrusion of the optic canal into the sphenoid sinus.[4] In all of these cases, an extremely thin bony shell surrounded the nerve, and pneumatization of the ipsilateral anterior clinoid process was present. In the case described by Som et al,[2] it was inferred that pressure was transmitted through an intact but thinned bony sinus wall.

Other conditions known to cause visual loss as a result of sinus disease include the orbital apex syndrome which occurs in the setting of acute sphenoethmoiditis and is manifested by visual loss and ophthalmoplegia without signs of orbital pathology such as proptosis, chemosis, or lid edema.[5] Unlike the case presented previously, that condition is caused by the contiguous spread of infection into the orbital apex. In such cases, the compression and inflammation within the orbital apex result in a poor prognosis, with permanent visual loss being the usual outcome even with medical and surgical intervention.[5]

Visual loss resulting from sphenoethmoid mucoceles and, more rarely, sinus neoplasms also have been reported.[6,7] Mucoceles impinge on the optic nerve directly through a defect in the bony wall of the optic canal, either by absorption that occurs from expansion of the mucocele or erosion secondary to inflammation from infection originating in the mucocele, commonly referred to as a mucopyocele.[6] Unlike the case presented previously, visual changes caused by infection, mucoceles, or neoplasms, while capable of transience at least initially, would not be expected to be related to altitude.

Conclusion

Sphenoid sinus pneumoceles are rare but have the potential for significant morbidity, including pressure headaches, visual disturbances, and even blindness. The diagnosis may be delayed, as in the patient described who saw several specialist physicians prior to the confirmatory diagnosis and definitive therapeutic intervention. Any symptoms linked with altitude changes should raise the consideration of alternobaric related pathophysiology such as a sinus pneumocele.

REFERENCES

1. Bell AF, Ivan DJ, Munson RA. Barosinus pneumocele: transient visual loss due to sphenoid sinus pneumocele in a U.S. Air Force pilot. Aviat Space Environ Med 1995; 66:276–279

2. Som PM, Sachdev VP, Biller HF. Sphenoid sinus pneumocele: report of a case. Arch Otolaryngol 1983; 109:761–764

3. Sugita K, Hirota T, Iguchi I, Kageyama N, Ito A. (1977) Transient amaurosis under decreased atmospheric pressure with sphenoid sinus dysplasia. J Neurosurg 1977; 46:111–114

4. Dessi P, Moulin G, Castro F, Chagnaud C, Cannoni M. Protrusion of the optic nerve into the ethmoid and sphenoid sinus: prospective study of 150 CT studies. Neuroradiology 1994; 36:515–516

5. Tarazi AE, Shikani AH. Irreversible unilateral visual loss due to acute sinusitis. Arch Otolaryngol Head Neck Surg 1991; 117:1400–1401

6. Moriyama H, Hesaka H, Tachibana T, Honda Y. Mucoceles of ethmoid and sphenoid sinus with visual disturbance. Arch Otolaryngol Head Neck Surg 1992; 118:142–147

7. Maniglia AJ, Kronberg FG, Culbertson W. Visual loss associated with orbital and sinus diseases. Laryngoscope 1984; 94:1050–1059

Salmonella enteritidis Infections from Shell Eggs: Outbreaks in California

JANET C. MOHLE-BOETANI, MD
S. BENSON WERNER, MD, MPH
SHARON ABBOTT
Berkeley, California
NANCIE BENDANA, PHN
Los Angeles, California
RAYMOND BRYANT
Berkeley, California
MARTIN FENSTERSHEIB, MD, MPH
Santa Clara, California
MICHELE GINSBERG, MD
LOUISE GRESHAM, PHD, MPH
San Diego, California
JANE KOEHLER, DVM
Atlanta, Georgia
LAURENE MASCOLA, MD
Los Angeles, California
For the investigative team

IN CALIFORNIA, BOTH the number of *Salmonella enteritidis* (SE) cases and the proportion of *Salmonella* cases due to the SE organism have increased markedly. SE cases increased from 594 in 1990 to 2,495 in 1995. Prior to 1990, less than 10% of *Salmonella* isolates were SE but since 1994 this proportion has been >25%.

Intact shell eggs can contain SE because infection of a chicken's reproductive tract can result in contamination prior to shell formation[1]; also, *Salmonella* can penetrate intact shells. Isolation of the organism from eggs is a rare event even when eggs from flocks implicated in outbreaks are tested. The prevalence of SE infection in eggs is estimated to be 1 in 10,000;[2] only 1% of eggs from infected chickens contain SE.[3] Sporadic SE infections have been associated with eating raw or undercooked eggs.[4–8] Outbreaks of SE infections have occurred primarily in the northeastern United States.[9]

We now present the first outbreak investigations in California that found a definitive association between SE disease and egg consumption and that first isolated SE in intact eggs epidemiologically linked to human disease in California. We also present the results of a survey of egg handling practices among food services, such as hospitals and restaurants, in one California county and summarize recent SE outbreaks in California.

Background

Between January and March 1993, three SE outbreaks were identified in noncontiguous counties in California, two in the southern and one in the northern part of the state. In Los Angeles County, 4 patients with SE infections ate at Deli A between December 26, 1992, and January 6, 1993, in the 5 days before the onset of illness; 1 person was hospitalized. In San Diego County, 11 patients with SE infections ate at Restaurant A on February 16, 1993, within 5 days before the onset of illness; 2 were hospitalized. In Santa Clara County, 22 patients with SE infections ate food from Sandwich Shop A between February 28 and March 4, 1993, within 3 days before the onset of illness; 3 were hospitalized.

Methods

Epidemiologic Studies

To identify food items associated with these outbreaks, case-control studies were conducted. Case patients had either laboratory-confirmed SE infections or illness compatible with salmonellosis; controls had no gastrointestinal symptoms during the time frame that laboratory-confirmed cases were symptomatic. Nonlaboratory-confirmed case patients and controls were meal companions of laboratory-confirmed case patients or a convenience sample of patrons who ate at the implicated restaurant during the same time frame as laboratory-confirmed case patients. In Los Angeles and San Diego, patrons were identified through credit card receipts; in Santa Clara patrons were identified by asking Sandwich Shop A customers if they purchased food during the appropriate time frame.

Environmental and traceback studies

Food handling practices were reviewed in the implicated restaurants in the week after the outbreaks were

(Mohle-Boetani JC, Werner SB, Abbott S, et al. *Salmonella enteritidis* infections from shell eggs: outbreaks in California. West J Med 1998; 169:299–301)

From the Disease Investigation and Surveillance Branch, Division of Communicable Disease Control, California Department of Health Services (Dr Mohle-Boetani, Dr Werner);

Microbial Diseases Laboratory, California Department of Health Services (Ms Abbott, Mr Bryant); County of Los Angeles, Department of Health Services (Ms Bendana, Dr Mascola);

Disease Control and Prevention Unit, Santa Clara County Health and Hospital Systems (Dr Fenstersheib); County of San Diego, Department of Health Services (Dr Ginsberg, Dr Gresham); Epidemiology and Prevention Branch, Georgia Department of Human Resources (Dr Koehler).

Reprints requests to J. Mohle-Boetani, MD, Disease Investigation and Surveillance Branch, Division of Communicable Disease Control, California Department of Health Services, 2151 Berkeley Way, Room 708, Berkeley, CA 94704.

Members of the Investigation Team are: Donnell Ewert, Sharon Lew, Karen Coy, Jeff Gans, Paula Tanner, Susan Hunt, Greg Inami, Josephine Jarvis.

(Preliminary results of this investigation were published in: CDC. Outbreaks of *Salmonella enteritidis* gastroenteritis—California, 1993. MMWR 1993; 42:793–796.)

ABBREVIATIONS USED IN TEXT

CI = Confidence Interval
MDL = Microbial Diseases Laboratory
RR = Relative Risk
SE = Salmonella enteritidis

identified; time and temperature measurements were recorded. Invoices of food bought in the month prior to consumption of suspected food items were reviewed in an effort to trace implicated food items back to their distributors and suppliers.

In Los Angeles, samples of pooled eggs and intact shell eggs, environmental swabs from containers, utensils, and surface areas used to pool eggs, and rectal swabs from 43 food handlers were collected (>1 month after the outbreak). In Santa Clara, on the day the outbreak was identified (March 11), samples of sandwich ingredients—mayonnaise, onion, chile, shredded carrots, soy sauce, and fish sauce—and intact shell eggs from the shipment used to prepare mayonnaise during the outbreak period were collected for laboratory studies. All 14 employees submitted stool specimens for culture.

Laboratory studies

Salmonella isolates from stool specimens were submitted by the initial laboratories to the county health department laboratories, and then to the state's Microbial Diseases Laboratory (MDL) for definitive serotyping, as required by state regulations. In the state's MDL, shells of eggs from the implicated restaurant in Los Angeles County and the sandwich shop in Santa Clara County were cultured for organisms before disinfection; the shells from all eggs from Santa Clara county were tested as one composite. Intact shell eggs were aseptically broken and the contents were pooled into composites of nine to ten eggs per pool, placed in enrichment culture, and screened for the SE organism using a BioControl 1-2 test kit.[10] The organism was isolated and identified in a standard fashion.

In the state's MDL, plasmids from SE isolates were extracted by alkaline lysis,[11] electrophoresed in 0.75% agarose gels, stained in ethidium bromide, excited by UV light, and photographed. The plasmid type of 22 SE isolates from the 37 outbreak cases (6 from Los Angeles, 10 from San Diego, and 6 from Santa Clara counties) were compared to the isolates from eggs from the Santa Clara outbreak and to the isolates from sporadic cases in California. Sporadic cases were SE-infected patients who were not part of these outbreaks and either resided in the three counties with outbreaks (n = 16) or resided in other counties (n = 24). The isolates from 8 patients in the outbreak (2 to 3 from each county) and from implicated eggs were phage typed by Frances W. Brenner at the Centers for Disease Control and Prevention.[12]

Food Service Survey

Food service managers from 93 restaurants and 3 hospitals in Santa Clara County with a similar number of employees (6 to 24) as Sandwich Shop A answered questions by telephone about their knowledge of pasteurized eggs and their use of such eggs versus shell eggs in dishes that called for pooled raw or undercooked eggs.

Results

Epidemiologic studies

In all three outbreaks only egg-containing dishes were statistically associated with illness (Table 1). In Los Angeles, 5 (83%) of the 6 case patients had eaten a lightly cooked egg dish (omelette, scrambled eggs, or egg salad) compared with 16 (16%) of 103 controls (odds ratio [OR] = 27.2). In San Diego, 18 (78%) of 23 case patients, but only 3 [12.5%] of 24 controls, ate food served with hollandaise sauce or bearnaise sauce (OR = 25.2). In Santa Clara, 100% of 38 case patients versus 22 (71%) of 31 controls ate a sandwich (OR = undefined) and 100% of case patients versus 18 (58%) of 31 controls ate a sandwich with mayonnaise spread (OR = undefined).

Environmental Studies

In Los Angeles Deli A, 22–30 eggs were pooled several times a day, added to a 2-quart container, and held at 50° F until they were used for lightly cooked egg dishes; the egg salad was stored at 60° F. In San Diego Restaurant A, 24 pooled egg yolks for hollandaise or bearnaise sauces were held under a heat lamp for up to 3.5 hours at 100° F to 120° F. In Santa Clara Sandwich Shop A, eggs for the mayonnaise were stored for several days prior to preparation in a room where the ambient temperature was 75° F to 80° F at the time of the inspection. The mayonnaise was prepared daily by cracking and separating the yolks of 15 to 60 eggs by hand and mixing the yolks in a blender with soy bean oil, sugar, salt, and garlic powder. After preparation, which took about 40 minutes, the mayonnaise was refrigerated at 42° F to 44° F. The pH of a sample of mayonnaise was 6.0.

Laboratory Studies

SE was isolated from one of five pools, each containing 9 to 10 grade AA eggs, from Sandwich Shop A in Santa Clara County. The culture of the composite of egg shells from Sandwich Shop A did not reveal *Salmonella*. Mayonnaise collected from Sandwich Shop A on March 11 (1 week after the illness onset of case patients) did not grow SE; no other sandwich ingredients from Sandwich Shop A were cultured. The organism was isolated from the stool of two foodhandlers who consumed mayonnaise during the outbreak period but denied symptoms. None of the food, environmental, or foodhandler specimens from Los Angeles County grew SE.

The plasmid profile of the SE isolate from pooled eggs from Sandwich Shop A was identical to that of case patients from all three outbreaks; in addition to the 38 MD virulence plasmid, all isolates had a 4 MD plasmid. Although the 38 MD virulence plasmid is found commonly among SE isolates, the 4 MD plasmid is not common in SE isolates in California. Of 40 strains from spo-

TABLE 1. *Summary of the first three Salmonella enteritidis outbreak investigations in California that found an association definitively associated with shell eggs, 1993.*

County (type of food service)	Case-patients: total (culture-confirmed)	Case- patients: hospitalized	Controls	Food items associated with illness	Odds Ratio (95% confidence interval)	P value
Los Angeles (Deli)	6 (4)	1	103	egg dishes (scrambled eggs, omelette, or egg salad)	27.2 (2.7–1300)	0.001
San Diego (Restaurant)	23 (11)	2	24	hollandaise or bearnaise sauce	25.2 (4.4–170.7)	<0.001
Santa Clara (Sandwich Shop)	38 (22)	3	31	sandwiches	undefined (lower limit = 3.0)	<0.001
				sandwiches with mayonnaise (restaurant-made)	undefined (lower limit = 5.5)	<0.001
Total	67 (37)	6				

radic cases identified in California in 1992 and 1993, only 8 had the two-band plasmid profile identical to the outbreak-associated strain; this proportion is significantly less than the proportion of outbreak isolates with this profile (20% versus 100%, $P < 0.0001$). The SE isolates from the egg and all eight randomly selected case patients from our outbreaks were phage type 13a, whereas in 1993 only 4% of SE isolates in California were phage type 13a.

Traceback Investigation

Review of restaurant invoices revealed that grade AA eggs from distributor Z were used to prepare the egg dishes implicated in all three outbreaks. This distributor received eggs from several sources and 70% were purchased from other states; one was an egg producer in the Midwest implicated in a phage type 13a outbreak.[13] However, traceback of contaminated eggs to their farm of origin was not possible for several reasons: Neither the eggs nor their cartons were labeled or coded as to their origin, eggs were not stored by the distributor or distributed in a systematic fashion that permitted traceback, and Federal traceback regulations prohibited traceback efforts when implicated eggs could have originated from more than a single ranch.

Food Service Survey

In Santa Clara County, the 94 food service managers (98% of 96 contacted) who participated in the study included 50 managers of nonchain restaurants, 41 of chain restaurants, and 3 of hospital food services. Managers from 2 nonchain restaurants refused participation. Of these 94 participants, 68 (72%) reported that they used eggs.

Hospitals were more likely to use pasteurized eggs compared with restaurants (100% versus 17%, Relative Risk [RR] = 5.9, 95% Confidence Interval [CI] = 3.5–10.1, $P = 0.007$). Chain restaurants were more likely than nonchain restaurants to ever use pasteurized eggs (33% versus 3%, RR = 11.7, 95% CI = 1.6–86.0, $P = 0.001$); 10% (3 of 30) of chain restaurants used pasteurized eggs exclusively.

Lightly cooked pooled egg dishes such as scrambled eggs, omelettes, and French toast were served by 25 food services. All 3 hospitals used pasteurized eggs exclusively for these egg dishes compared with only 9% (2 of 25) of restaurants. All of the 25 restaurants that made sauces with gently heated eggs (such as bearnaise or hollandaise sauce) or raw eggs (such as mayonnaise and Caesar's salad dressing) used shell eggs for these sauces; no hospitals made sauces with gently heated or raw eggs. Chain restaurants were more likely than nonchain restaurants to serve lightly cooked pooled eggs (59% versus 24%, RR = 2.3, 95% CI = 1.2–4.4, $P = 0.008$) and less likely to serve sauces with raw eggs (10% versus 37%, RR = 0.27, 95% CI = 0.08–0.86, $P = 0.01$). Restaurants that served sauces with raw shell eggs had higher customer charges (median = $15, range $3–$50) than restaurants that did not (median = $6, range $3–$33, $P < 0.001$).

Only 35% (24 of 68) of food service managers who used eggs reported knowing that pasteurized eggs could be substituted for shell eggs in recipes that required raw, gently heated, or lightly cooked pooled eggs. Managers who knew that substitution with pasteurized eggs was possible yet used shell eggs in dishes with raw or undercooked eggs reported concern about the attendant cost, preparation time, and the customers' perceptions of pasteurized eggs.

Discussion

These investigations add to the increasing body of evidence that outbreaks of human SE infections are associated with shell eggs. These are the first investigations of SE outbreaks (as distinct from sporadic SE cases[4]) in California, associated with shell eggs, in which SE isolates from case patients and egg contents were identical by both plasmid and phage typing. The fact that a culture of the egg shells alone did not grow SE, while the contents of the eggs did, strongly suggests that the contamination occurred prior to shell formation by transovarian transmission; accordingly, disinfection of these egg shells would not have prevented their contamination or prevented these outbreaks. Consistent with our epidemiologic findings, a case-control study of sporadic SE cases in Los Angeles County[4] identified eating undercooked or raw eggs as a risk factor.

A single source for the contaminated eggs as the cause of all three outbreaks is suggested by these factors: The same unusual combination of phage and plasmid profile types—with both a common 38 MD virulence plasmid and an uncommon 4 MD plasmid—identical among cases from all three outbreaks and from eggs used to make mayonnaise consumed by case patients, the temporal clustering of the outbreaks, and a common distributor of all implicated eggs for all 3 outbreaks.

These results illustrate how shared findings from investigations of temporally-associated outbreaks of SE or other infections occurring in noncontiguous geographic areas can provide an opportunity to identify a common source. Cooperation among public health and environmental health departments is essential for the success of such investigations.

Since these outbreaks, many other SE outbreaks associated with eggs have occurred. Of the 53 outbreaks reported to the California Department of Health Services in 1993–1997, 22 (42%) had a vehicle confirmed through isolation of SE from a food item or by a statistically significant association in an epidemiologic study. An egg dish was the confirmed vehicle in 18 (82%) of these outbreaks. These proportions are nearly identical to those found in a national study of SE outbreaks where 44% of SE outbreaks had confirmed vehicles and 82% of confirmed vehicles were egg dishes.[9] Among egg dishes that were confirmed vehicles in California, 44% were traditionally prepared (for example, scrambled eggs and omelettes), 6% should have contained fully cooked eggs (such as quiche and lasagna), 11% used eggs that were gently heated (such as hollandaise sauce and mousse), and 39% used raw eggs (for example, mayonnaise and ice cream); 69% of these egg dishes were prepared by commercial establishments.

Prevention of SE outbreaks will require both control of contamination at the farm level and safe egg-handling practices. In these outbreaks a complete traceback, with testing of the farm and diversion of eggs until the farm was decontaminated, could not be done. Traceback investigations could be facilitated by labeling of eggs or egg cartons as to the farm of origin, and some in the United States egg industry are promoting this practice.

To reduce the risk of producing eggs contaminated with SE, the egg industry, state and federal governments, and academia jointly developed the California Egg Quality Assurance Plan in 1994. This voluntary program for farms and processing facilities emphasizes safe production and processing practices such as biosecurity, rodent control, and flock health management. To minimize proliferation of SE within shell eggs prior to their sale, California law now requires that shell eggs be stored, transported, and displayed at 45° F or lower.

In addition, there should be safer egg handling by consumers and food services. In 1990, which was 3 years before our food service survey was conducted, shell eggs were designated a potentially hazardous food by the federal Food and Drug Administration (FDA). The FDA recommended thorough cooking of eggs and the substitution of commercially pasteurized eggs for shell eggs in recipes that call for raw or undercooked eggs. Yet, both the environmental investigations that followed these outbreaks and our food service survey found that pasteurized eggs were underutilized. In all three outbreaks, the opportunity for *Salmonella* to multiply was increased by foodhandling errors such as pooling of raw eggs and maintaining them above 45° F, holding gently heated pooled eggs at <140° F, and storing eggs used for mayonnaise at ambient temperatures. In the food service survey, a high percentage of restaurants posed a risk to the public by using pooled shell eggs for raw or undercooked egg dishes. Although the sample size was small, hospitals were more likely than restaurants to use pasteurized eggs, suggesting that recommendations on the preferred use of these eggs has reached this type of food service. The use of pasteurized eggs in restaurants should be promoted, especially in nonchain restaurants, where, in our study, only 3% used pasteurized eggs. The egg dishes identified as confirmed vehicles in SE outbreaks reported in 1993–1997 in California also illustrate the ongoing, hazardous practice of serving raw or undercooked shell eggs rather than pasteurized eggs.

Until SE in eggs can be controlled or eliminated, foodhandling facilities, physicians, and consumers should be aware of ongoing disease and outbreaks in California and in other western states.[14] Consumers should use the guidelines listed in Table 2 to reduce the risk of disease from contaminated eggs. To monitor the impact of implementing these guidelines, egg use surveys could be conducted for both consumers and restaurants. Clinicians should obtain stool cultures for *Salmonella* from all patients with diarrhea and fever, and all culture-confirmed cases should be reported to local health departments and isolates sent to the public health laboratory for serotyping. All of these precautions are necessary to curtail the SE epidemic associated with eggs in the western United States.

Acknowledgment

We thank Dr. Robert Tauxe for his suggestions on conducting the food services survey.

REFERENCES

1. St. Louis ME, Morse DL, Potter ME, et al. The emergence of grade A eggs as a major source of *Salmonella enteritidis* infections: new implication for control of salmonellosis. JAMA 1988; 259:2103–2107

2. CDC. Update: *Salmonella enteritidis* infections and shell eggs—United States, 1990 MMWR. 1990; 39(50): 909–912

3. Humphrey TJ, Baskerville A, Mawer S, Rowe B, Hopper S. *Salmonella enteritidis* phage type 4 from the contents of intact eggs: a study involving naturally infected hens. Epidemiol Infect 1989; 103:415–423

4. Passaro DJ, Reporter R, Mascola L, et al. Epidemic *Salmonella enteritidis* infection in Los Angeles County, California—The predominance of phage type 4. West J Med 1996; 165:126–130

5. Hedberg CW, David MJ, White KE, MacDonald KL, Osterholm MT. Role of egg consumption in sporadic *Salmonella enteritidis* and *Salmonella typhimurium* infection in Minnesota. J Infect Dis 1993; 167:107–111

6. Morse DL, Birkhead GS, Guardino J, Kondracki SF, Guzewich JJ. Outbreak and sporadic egg-associated cases of *Salmonella enteritidis*: New York's experience. Am J Public Health 1994; 84:859–860

TABLE 2. *Recommendations for Reducing the Risk of Salmonella enteritidis from Shell Eggs*

1. Shell eggs should be transported, and stored at an internal temperature of 45° F or below.
2. Shell eggs should be protected from possible contamination by other raw foods such as raw meat.
3. Stocks of shell eggs should be rotated - first in, first out, and ideally should be used within 21 days.
4. Only clean uncracked eggs should be used.
5. Hands should be washed with soap and water before and after using shell eggs.
6. All blenders and utensils that come in contact with raw eggs should be dismantled and washed before using them again.
7. Pooled shell eggs should be cooked immediately and not be held (restaurants should not pool eggs and then cook them to order as scrambled eggs or omelettes, over several hours).
8. Individually prepared eggs and pooled eggs should be cooked to 140° F or above; both the yolk and egg white should be firm and not runny.
9. If not eaten immediately, cooked eggs and egg dishes should either be held at an internal temperature of >140° F or be refrigerated at <40° F.
10. Raw eggs should not be used as an ingredient in the preparation of uncooked or gently heated, ready-to-eat menu items such as Caesar's salad dressing, hollandaise or bearnaise sauce, mayonnaise, eggnog, ice cream, and egg-fortified drinks.
11. Raw eggs should not be used as an ingredient of lightly cooked foods (such as soft custards, meringues, French toast, and Monte Christo sandwiches).
12. Pasteurized eggs should be substituted for shell eggs when preparing lightly cooked egg dishes (scrambled eggs, omelettes), use in gently heated sauces containing eggs (bearnaise or hollandaise sauce), and recipes with eggs that do not require cooking (mayonnaise, ice cream, tartar sauce, egg-fortified drinks).

7. Coyle EF, Palmer SR, Ribeirio CD, et al. *Salmonella enteritidis* phage type 4 infection; association with hen's eggs. Lancet 1988; 2:1295–1296

8. Cowden JM, Lynch D, Joseph CA, et al. Case-control study of infections with *Salmonella enteritidis* phage type 4 in England. Br Med J 1989; 299:771–773

9. Mishu B, Koehler J, Lee LA, et al. Outbreaks of *Salmonella enteritidis* infection in the United States, 1985–1991. J Infect Dis 1994; 169:547–552

10. Association of Analytical Chemists. In: Official Methods of Analysis, 15th ed. sec 989.13 Arlington, VA: AOAC, 1990

11. Birnboim HC, Doly J. A rapid alkaline extraction procedure for screening recombinant plasmid DNA. Nucleic Acid Res 1979; 7:1513–1523

12. Ward LR, deSa JDH, Rowe B. A phage typing scheme for *Salmonella enteritidis*. Epidemiol Infect 1987; 99:291–294

13. Altekruse S, Koehler J, Hickman-Brenner F, Tauxe RV, Ferris K. A comparison of *Salmonella enteritidis* phage type from egg associated oubreaks and implicated laying flocks. Epidemiol Infect 1993; 110:17– 22

14. Centers for Disease Control and Prevention. Epi-Aid 96-16 Trip Report: Investigation of increased incidence of *Salmonella enteritidis* isolates in Utah (unpublished public document)

Topics in Primary Care Medicine

Cervical Cancer: Developments in Screening and Evaluation of the Abnormal Pap Smear

JUDITH M.E. WALSH, MD, MPH, *San Francisco, California*

Of the more than 50 million Pap smears performed annually in the United States, about 5% of them are abnormal. Although the need for treatment of high-grade lesions is clear, the appropriate management of low-grade lesions remains controversial. New methods of screening for cervical cancer have become available, including testing for the human papilloma virus and improved methods of administering and evaluating the Pap smear. This review addresses new developments in cervical cancer screening and management strategies for when an abnormality is detected.

(Walsh JME. Cervical cancer: developments in screening and evaluation of the abnormal Pap smear. West J Med 1998 169:304–310)

The incidence of invasive cervical cancer has decreased by 70% in the last 40 years, in large part due to routine use of Papanicolaou (Pap) smear screening. Risk factors for cervical cancer include early age at first intercourse, history of multiple sexual partners, and smoking.[1–4] The U.S. Preventive Services Task Force recommends that cervical cancer screening be performed in all women with a cervix who are or have been sexually active. Cervical cancer screening should begin at the onset of sexual activity and should be repeated at least every 3 years.[5] Other groups (including the American Cancer Society, the National Cancer Institute, the American College of Obstetricians and Gynecologists, the American Academy of Family Physicians, and the American Medical Association) recommend annual screening beginning at age 18 or the onset of sexual activity.[6] Once three consecutive smears have been negative, screening may be performed less frequently at the discretion of the physician. It is appropriate to continue annual screening in women considered to be at high risk for cervical cancer based on the risk factors described above.

The U.S. Preventive Services Task Force acknowledges that although there is insufficient evidence to recommend an upper age limit for discontinuation of screening, recommendations can be made on other grounds to discontinue screening in women over 65 who have had consistently normal smears.[5,7] Many older minority women may not have had previous regular screening,[8] however, so continued screening is important for them.[9,10]

More than 50 million Pap smears are performed annually in the United States,[11] and about 5% of them are abnormal. Although the need for treatment of high-grade lesions is clear, the appropriate management of low-grade lesions remains controversial. Morbidities are associated with evaluation and treatment of low-grade lesions, and it is not clear whether treating them has a significant impact on the development of cervical cancer. In recent years, the costs of evaluating low-grade cervical lesions have increased dramatically. One study of university and commercial cytologic labs indicated a 5% rate of low-grade cytologic abnormalities. To evaluate colposcopically and treat all those abnormalities would cost $6 billion per year.[12]

New methods of screening for cervical cancer have become available, and primary care clinicians must decide whether and when it is appropriate to use them. In addition, when confronted with an abnormal Pap smear, the clinician must know whether to refer to a gynecologist immediately, whether and when to repeat the Pap smear, and how to counsel the patient on the meaning of the abnormality.

Classification of Pap Smears

The Bethesda System, developed in 1988, is the current system of classification of Pap test results. It assesses the following factors: adequacy of specimen, general categorization, and descriptive diagnosis. Squamous intraepithelial lesion (SIL) is the Bethesda System's terminology for dysplasia. Squamous cell abnormalities are divided into three categories: atypical squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesions (LGSIL), and high-grade squamous intraepithelial lesions (HGSIL). Table 1 displays the relationship of the older diagnoses to the new system.

From the Division of General Internal Medicine, University of California, San Francisco.
Reprint Requests to Dr. Walsh, UCSF/Division of General Internal Medicine, Box 1732, 1701 Divisidero Street, San Francisco, CA 94115 (e-mail: jmwalsh@itsa.ucsf.edu).

ABBREVIATIONS USED IN TEXT

AGUS = atypical glandular cells of undetermined significance
ASCUS = atypical squamous cells of undetermined significance
CIN = cervical intraepithelial neoplasia
HGSIL = high-grade squamous intraepithelial lesions
HPV = human papilloma virus
LGSIL = low-grade squamous intraepithelial lesions
VAIN = vaginal intraepithelial neoplasia

The aggressiveness of the approach to evaluating a Pap smear abnormality depends on what would happen if a histologic abnormality existed and were *not* treated. Many studies have tried to describe the natural history of cervical intraepithelial neoplasia (CIN), and all have had methodologic limitations. Ostor[13] critically analyzed and summarized the studies and developed the estimates displayed in Table 2. Many lesions will regress spontaneously, especially those in the CIN I category (now classified as LGSIL). More than half of CIN I lesions will regress spontaneously, as will more than one-third of even the more aggressive CIN III lesions. In addition, even if low-grade lesions do not regress, very few (1% of CIN I lesions) will progress to invasive cervical cancer. Since so many low-grade lesions will resolve without treatment, the utility of early, aggressive treatment may be less than was previously assumed.

New Screening Technologies

Several new tests for the detection and evaluation of cervical cancer and its precursors have become available. The new technologies aim to detect abnormalities earlier, assess lesion severity so as to predict those that are most likely to progress to invasive cervical cancer, and decrease the false-negative rate (the proportion of abnormal Pap smears which are incorrectly read as normal). The new tests include screening for human papilloma virus (HPV) infection, typing of HPV in Pap smear specimens, improved methods for preparation of the cervical smear (ThinPrep), and automated technologies for rescreening Pap smears initially read as negative (PAPNET and AutoPap).

Screening for HPV infection

Since HPV is known to play a causative role in the development of cervical cancer, detection of HPV infection could theoretically be important in cervical cancer screening, by enabling earlier detection of abnormalities before cytologic changes occur. The natural history of the progression of HPV infection to cervical cancer is poorly understood, however.[14] Several HPV viral DNA detection technologies are available, including dot blot hybridization, Southern blot hybridization, in situ hybridization, Hybrid Capture test, and polymerase chain reaction. ViraPap is a DNA-binding assay that detects small amounts of viral DNA in Pap smears. In one study of patients at high risk (history of condyloma, abnormal Pap, sexual partner with warts), the sensitivity of ViraPap in predicting colposcopic abnormalities was 61.5% and the specificity was 70%, unfortunately not accurate enough to decrease the need for colposcopy.[15] No prospective screening studies of ViraPap have been done; most of the studies of ViraPap have been on those with atypia. An additional factor that probably limits the predictive value of screening for viral DNA is the high prevalence of HPV infection in young women, especially since the percentage of women with positive tests who will develop cervical cancer is unknown.[16]

TABLE 1.—*The Bethesda System and Its Relationship to Prior Papanicolaou Classifications*

Low-Grade Squamous Intraepithelial Lesion (LGSIL)
Koilocytic atypia
Condyloma
CIN I
Mild dysplasia
High-Grade Squamous Intraepithelial Lesion (HGSIL)
CIN II and CIN III
Moderate and severe dysplasia
Carcinoma in situ

HPV Typing

Almost all (90%) of cervical dysplasias are associated with HPV. Some studies have shown an association between certain HPV types and lesion persistence or progression[17–19]; others have not.[20,21]

HPV types have been divided into several categories. The low-risk category includes those HPV types that have been strongly associated with LGSIL, rarely associated with HGSIL, and never associated with cancer (HPV 6, 11, or in the 40s). Intermediate-risk types have been strongly associated with HGSIL (HPV 31, 33, 35, 51, 52). Those in the high-risk category (HPV 16, 18, 45, 56) have been strongly associated with HGSIL and cervical cancer.[22–27]

Theoretically, HPV typing could be used in patients with atypical Paps to predict women at low or high risk for developing dysplasia, but this has not been the case in practice. Goff and colleagues[28] performed HPV typing on 171 consecutive patients at a colposcopy clinic. Of the 28 with atypia and high-risk HPV types, only 6 (21%) had cervical intraepithelial neoplasia. An ongoing National

TABLE 2.—*Natural History of Cervical Intraepithelial Neoplasia*

	Regress	*Persist*	*Progress to CIS*	*Progress to invasion*
CIN I	57	32	11	1
CIN II	43	35	22	5
CIN III	32	<56	—	>12

CIS = carcinoma in situ
—
Data are %.

Cancer Institute trial will assess whether HPV typing is helpful in the management of cervical dysplasia.

In summary, neither screening for HPV infection or HPV typing is useful at this time in screening for cervical cancer or predicting risk of dysplasia. Even if it were, there is no treatment for HPV detected in this way, so screening recommendations would not change—periodic sampling of cervical cells for either cytologic evaluation or viral DNA testing would still need to be performed. HPV typing has not yet been proven to accurately predict disease progression, and so is currently not clinically useful in detecting women at high risk for cervical cancer. In the future, HPV technologies may be useful in the triage of patients with ASCUS or in determining which patients with mild or moderate dysplasia can avoid unnecessary colposcopies.[29]

Automated Technologies

Decreasing the false-negative rate of Pap smears has been a major concern in recent years. Pap smear errors (errors in sampling, preparation, and interpretation) can occur anywhere from collection by the clinician to interpretation by the pathologist. Several new technologies are designed to decrease those errors. ThinPrep addresses those errors which occur during preparation of the smear whereas PAPNET and AutoPap address those errors which occur during interpretation of the smear.

Cervical Smear Preparation (ThinPrep)

The goal of ThinPrep is to prepare high-quality slides with a representative number of cells for review, and thereby reduce the number of abnormalities missed during initial screening. The cervical sampling device is rinsed into a buffered preservative solution, preserving most of the sampled cells. They are then passed through a filter, which separates them from unwanted white cells, red cells, and other debris. Cells are then placed from the filter onto a glass slide, which results in a uniformly thin layer of cells that is easier to review, increasing the reviewer's ability to detect abnormalities. Use of ThinPrep results in a 65% increase in the number of abnormal cells identified compared with the standard Papanicolau screening.[30] In addition, two studies have shown that use of ThinPrep is associated with a higher proportion of satisfactory slides.[31,32]

Only one study comparing ThinPrep with conventional smears compared both with the gold standard of colposcopic biopsy.[33] The sensitivity of ThinPrep for the detection of LGSIL or more severe lesions was slightly higher than the sensitivity of the conventional smear (73.6 versus 67.3%, $P = 0.034$). Importantly, the specificities of the two tests (the ability to correctly identify normal smears as normal) were not significantly different. The FDA has approved the use of ThinPrep and permits ThinPrep to call itself "significantly more effective" than previous methods. Compared with conventional Pap smears, ThinPrep improves diagnostic sensitivity (the ability to detect pathology) without a major change in specificity. In high-prevalence populations, an increase in sensitivity will only slightly increase detection of disease, but in low-prevalence populations (<5% LGSIL), which are typical in most of the United States, any small increase in sensitivity will significantly increase the magnitude of disease detection. If ThinPrep facilitates the detection of LGSIL and more severe lesions, as was suggested in an early study,[34] it would probably be more beneficial than if it also increased the detection of minimally abnormal lesions, such as ASCUS, many of which will regress spontaneously. Decisions about the routine use of ThinPrep in clinical practice must balance the additional costs of ThinPrep with the potential benefits. The costs include not only the costs of ThinPrep itself, but also the costs of evaluating the increased numbers of lesions detected. The benefits may include improved disease detection as well as a decrease in the proportion of "unsatisfactory" smears.

Automated Pap Smear Rescreening

The goal of the automated rescreening technologies is to decrease false-negative test results. Since 1988, when the Clinical Laboratory Information Act was passed, all negative slides have been subject to rescreening. According to federal guidelines, at least 10% of negative smears must be rescreened. Two new computerized technologies for rescreening negative Pap smears (PAPNET and AutoPap) have recently been approved by the FDA. With PAPNET, slides to be rescreened are shipped to a PAPNET processing center where they are rescanned. Neural networks, capable of recognizing several factors simultaneously, analyze the cells, and PAPNET records video images of the abnormalities. The video images and the original slides are returned to the laboratory of origin, and selected slides are then reviewed by a cytotechnologist or pathologist.

With AutoPap, algorithmic image processing is used to identify abnormal cells. After a slide is processed, an evaluation score between 0 and 1.0 is generated. AutoPap rescreening can be done on site and seems to be particularly useful in selecting those slides that will undergo the mandatory 10% rescreening. Instead of the 10% of slides being randomly selected, they can be preferentially selected using AutoPap from those with a higher number of abnormalities.[35]

Use of both AutoPap and PAPNET has been shown to be superior to manual rescreening for the detection of false-negative smears.[36,37] Ideally, if the automated technologies could preferentially detect higher-grade lesions, which are more likely to progress, their utility in rescreening would be higher.

Future directions for research with the automated technologies include their role in primary screening and in evaluating minimally abnormal smears. In one study of 101 smears initially diagnosed as ASCUS, 24 of the 37 smears (65%) that showed histologic evidence of SIL were reclassified as either LGSIL or HGSIL using PAPNET-directed rescreening.[38] If automated technologies such as AutoPap or PAPNET are used for primary screening at some time in the future, an important question will be whether they can identify smears that may not need to be reviewed by the cytotechnologist.

Summary

The Pap smear is designed to screen for disease in populations and identify those patients who need colposcopy. It is not a test designed to diagnose disease in a particular individual. No screening test is 100% sensitive or 100% specific—there will always be false-positive and false-negative test results. Nonetheless, the Pap smear has been enormously successful in decreasing cervical cancer mortality.

Use of the automated technologies with their improved sensitivities will improve the rate of detection of false-negative smears, but it will also increase the false-positive rate. Whether the improved detection of cytologic abnormalities will lead to decreased morbidity and mortality is not yet known. Routine use of the automated rescreening technologies would markedly increase the costs associated with cervical cancer screening—PAPNET would be paid for by individuals and AutoPap by laboratories. Before they are used routinely, formal cost-benefit analyses must be performed.

Of the three types of errors in Pap smear screening—sampling error, diagnostic error, and failure to screen in the first place—the third is by far the most important. We must focus our efforts on ensuring screening for all appropriate women.

Management of Abnormal Cervical Cytology

In 1992, a workshop was convened by the National Cancer Institute to develop guidelines for the management of abnormal cervical cytology. There were several problems with the development of those guidelines, including limited experience with the Bethesda System, limited knowledge of the behavior of low-grade lesions, and limited clinical trial data regarding the efficacy of adjunctive screening methods such as HPV testing. Acknowledging those limitations, the workshop participants developed interim guidelines, published in 1994, and recommended that the guidelines should evolve as more information becomes available.[12]

High Grade Squamous Intraepithelial Lesion

HGSIL is very predictive of a high-grade lesion on the cervix. Patients with HGSIL should proceed immediately to colposcopy, endocervical curettage, and appropriately directed biopsies.[12]

Low Grade Squamous Intraepithelial Lesion

In the past, all CIN I lesions (now in the LGSIL category) were treated upon detection. Because many lesions will regress, that may not be necessary. Although the majority of LGSILs will spontaneously revert to normal, 20% to 50% of patients with LGSIL on Pap will have a higher-grade lesion on colposcopically directed biopsy.[39–43]

In Canada and the Netherlands, patients with LGSIL are followed with repeat Pap smears every 4–6 months for 2 years.[44,45] If LGSIL findings persist, the patient proceeds to colposcopy. Once three Pap smears in a row are normal, the patient returns to standard screening.

In the United States, most gynecologists opt for immediate colposcopy and biopsy. The goals of colposcopy are to fully examine the transformation zone, inspect acetowhite areas, perform a biopsy of abnormal-appearing areas, and sample the endocervical canal with curettage.

Identified lesions can be biopsied or followed colposcopically. Using colposcopy, a "directed biopsy" of any abnormality may be done. It is not appropriate to routinely biopsy normal-appearing areas of the transformation zone. If a lesion is entirely visible and the limits of the transformation zone are seen, it can be excised, ablated, or followed (in the case of LGSIL). If the lesion is not fully visible, cervical conization may be considered. Any lesion that is treated should be done so based on histologic evaluation.[12]

Since many lesions will regress on their own, following them colposcopically may spare therapy in a large percentage of women and can thereby decrease expense, discomfort, stress, and potential complications of therapy such as cervical stenosis or incompetence.[46] The disadvantages of following the lesion colposcopically include patient anxiety, inconvenience of multiple office visits, expense of repeated colposcopies, and the possibility that the patient will not attend all appointments.

In summary, options for the management of LGSIL include follow-up with frequent Pap tests with further evaluation for persistent abnormalities, colposcopy with directed biopsy and treatment of abnormalities, or colposcopic follow-up of low-grade lesions, many of which will regress spontaneously. Most U.S. gynecologists opt for colposcopy instead of frequent Pap follow-up.

Atypical Squamous Cells of Undetermined Significance

Atypical squamous cells of undetermined significance (ASCUS) are squamous cell abnormalities not attributable to reactive changes alone, but not completely typical of a squamous intraepithelial lesion.[12] Cervicovaginal infection is associated with an increased incidence of ASCUS on Pap smear.[47] When a specific cause (e.g., *Trichomonas* infection) can be identified, it is reported as benign reactive changes instead of ASCUS. In general, ASCUS should be expected in no more than 5% of the screened population; if it is reported in more, the diagnosis may be overused. The rate of ASCUS is usually about two to three times the rate of squamous intraepithelial lesions.

When confronted with a diagnosis of ASCUS, the clinician can either refer for immediate colposcopy or repeat the Pap in 3–6 months and refer for colposcopy if the Pap is still atypical. The advantage of waiting and repeating the Pap smear is that many atypias will resolve spontaneously. On the other hand, if the second Pap yields a false-negative result, a significant lesion may be missed. Given the very long preclinical phase of cervical cancer, however, even if a second Pap yields a false-negative result, a true abnormality is likely to turn up on a future Pap smear.

An ongoing clinical trial sponsored by the National Cancer Institute addresses whether the wait-and-see strategy is appropriate for women with ASCUS or LGSIL diagnoses. In the ASCUS/LGSIL Triage Study (ALTS), 7,200 women have been recruited and are being followed for 3 years at several sites. Women with Pap smear abnormalities are randomly assigned to one of three groups: watchful waiting with follow-up Pap every 6 months, immediate colposcopy with biopsy, and testing for HPV strains associated with a high risk of progression to cancer plus colposcopy for women with those high-risk strains. The trial also includes new ways to collect and read cervical specimens. Finally, cervicography (magnified photographs of the cervix) will be performed in all women in the trial at baseline and at 6-month intervals to ensure that lesions are not missed in women who do not receive colposcopy. Colposcopy will be offered to all women at the end of the trial.

Although data regarding the optimal management of ASCUS will not be available until the end of the trial, reasonable strategies for the management of ASCUS, as recommended by the National Cancer Institute,[12] include the following:

- Follow-up PAP without colposcopy, especially if the diagnosis is not qualified further or favors a reactive process. Paps should be repeated every 4–6 months for 2 years. If a second ASCUS occurs during the 2-year period, the patient should be considered for colposcopy.
- If the diagnosis of ASCUS is associated with severe inflammation, the patient should be reevaluated in 2–3 months. Any infection associated with the inflammation should be treated.
- The diagnosis of ASCUS in postmenopausal women has different implications—atrophic cells look like parabasal cells and look neoplastic. Treatment with estrogen creme before repeating the Pap smear may help in the differential diagnosis.
- If the diagnosis of ASCUS is associated with a qualifier that favors neoplasia, the patient should be managed as if she had a diagnosis of LGSIL.
- If a patient has a history of cervical dysplasia or there is concern about compliance, she may be referred directly to colposcopy.

Atypical Glandular Cells of Undetermined Significance (AGUS)

Abnormal glandular cells may be of either endometrial or endocervical etiology. Atypical glandular cells of undetermined significance are found in about 0.5% of Pap smears and are often associated with HGSIL.[48] The incidence of adenocarcinoma is increasing, especially in women under the age of 35.[49–51] Two recent case series have shown a high rate of significant gynecologic neoplasia in women with AGUS on cervical cytology.[52,53]

When endocervical cells are present on the smear, the diagnosis should indicate whether the changes are reactive or neoplastic and whether the cells are of endocervical or endometrial origin. The subtype diagnosis "suggestive of reactive" was a negative predictor of a significant lesion in one study.[52]

Until further studies elucidate the factors associated with an increased risk of neoplasia associated with AGUS, current recommendations are that all women with AGUS on Pap smear should undergo colposcopy and endocervical curettage.[12] If endocervical and endometrial sampling do not reveal a source for the abnormality, other sources such as ovary, colon, breast, or gastrointestinal tract should be considered.[54]

Absent Endocervical Cells

The location of squamocolumnar junction varies with age and fertility. Smears of patients in the reproductive age group tend to yield the most endocervical cells. Smears with endocervical cells have a higher rate of abnormalities than those without. However, longitudinal studies that followed women whose initial smears lacked endocervical cells did not show a higher rate of abnormalities on subsequent smears, which would be expected if the first smears were false-negatives.

Kivlahan and Ingram[55] studied 5,975 women who underwent at least two routine Pap smears from 1980 to 1984 and had a negative result on the first smear. There was no significant difference between rates of atypia on the second smear between those women who had endocervical cells present and those who did not (3.3% vs. 3.0%). Mitchell and Medley[56] studied 20,222 women who had initially negative smears. Again, there was no significant difference in subsequent cervical intraepithelial neoplasia in those having smears without vs. with endocervical cells. Joseph and colleagues[57] compared cytology with cervical colposcopic biopsies, cone biopsies, and hysterectomy specimens in 772 consecutive patients at a colposcopy clinic. The rate of detection of squamous abnormalities was not different between the two groups (90% in both groups). Among the slides that had no endocervical cells, however, the number of abnormal cells was less, and so more careful screening was required.

In summary, a lack of endocervical cells does not seem to be associated with a higher subsequent rate of cervical dysplasia. In average-risk patients with a prior history of adequate smears, a smear without endocervical cells does not need to be routinely repeated. It is probably prudent to repeat a smear if the woman is otherwise at increased risk for cervical dysplasia.

Pap Smear After Hysterectomy

About 25% to 30% of women in the United States undergo hysterectomy for benign disease. Since supracervical hysterectomy is not commonly performed, the need for continued Pap screening after hysterectomy has been questioned. According to the Pap Smear Adequacy Project, 13% of Pap smears are performed on women who have undergone hysterectomy.[58]

If the cervix has been removed, then any screening would be for vaginal cancer, vaginal intraepithelial neoplasia (VAIN), or preinvasive cervical pathology from "residual cervical tissue." Primary invasive vaginal cancer

is rare, accounting for only 250 deaths per year (cervical cancer accounts for about 4,000 deaths per year). Vaginal carcinoma in situ, which may be a precursor to vaginal cancer, is even less common. Cervical dysplasia and cervical cancer are risk factors for the development of vaginal cancer. Other risk factors include increased age, increased number of sexual partners, and possibly HPV infection, although vaginal cancer is extremely rare in women with no history of cervical dysplasia.

Some early case series, case control, and cohort studies suggested that vaginal hysterectomy for benign disease was associated with an increased incidence of vaginal malignancy, but those early studies had several flaws, including not completely controlling for a prior history of dysplasia, recall bias, lack of an appropriate control group, and inappropriate selection of a control group.[58] One of the most important problems was detection bias: since practitioners may be less likely to perform a scraping of the vaginal vault when the cervix is intact, women who have had a hysterectomy and are undergoing screening may be more likely to have VAIN detected compared with controls who are assumed not to have VAIN based on the results of previous cervical Pap smears.

Recently, Pearce and colleagues[59] analyzed vaginal cuff Pap smears in 6,265 women who had undergone hysterectomy for benign disease. In the estimated 5,682 women in follow-up, 9,610 Pap smears were performed. Only 104 of those (from 79 women) were abnormal, and over half of the abnormalities were ASCUS. Vaginal epithelial neoplasia was detected in only five women, and no cases of vaginal cancer were detected. Only 1.1% of all tests were abnormal, and the positive predictive value of an abnormal smear for vaginal cancer was 0% (95% confidence interval 0% to 30%).

Screening for vaginal cancer in women who have undergone hysterectomy for benign disease does not meet criteria for effectiveness of a screening test. The burden of suffering is very low, as it is a very rare cancer. The low prevalence of disease leads to a high false-positive rate; it has been estimated that less than 1% of patients testing positive by cytology have the disease.[60] There is currently no evidence that early detection is efficacious.[58] Therefore, due to the rarity of the disease and the low likelihood of detecting vaginal cancer with screening, women who have had a hysterectomy for benign disease should not undergo routine screening for vaginal cancer.

Conclusions

Routine Pap smear screening has markedly decreased cervical cancer mortality. New technologies such as HPV typing may ultimately be useful in triage of patients for more intensive evaluation, but further studies are needed. Other new technologies such as ThinPrep, AutoPap, and PAPNET are designed to decrease the number of false-negative Pap smears. None of the new technologies should replace standard Pap screening.

Appropriate treatment for abnormalities detected on Pap smear depends on the severity of the lesion and on what would happen if the lesion were left untreated. Any high-grade lesion detected on Pap smear should be evaluated by colposcopy, and HGSIL identified by biopsy should be treated. LGSIL can be biopsied and treated, followed colposcopically, or followed with frequent Pap smears. Frequent Pap follow-up is an appropriate strategy for women with ASCUS who are thought to be at low risk. Women with AGUS on Pap smear should be referred for colposcopy and endocervical curettage. Smears with absent endocervical cells need not be routinely repeated, and women who have had a hysterectomy for benign disease do not need continued Pap smears.

Finally, although efforts to improve the accuracy of screening are important, the biggest impact on cervical cancer mortality will come by ensuring access to cervical cancer screening for all women, particularly those who have previously been unscreened. We must also emphasize primary prevention, including decreasing high-risk behaviors (smoking, postponing the onset of sexual activity, limiting the number of sexual partners), and encouraging appropriate safe sexual practices including barrier contraception.

Acknowledgments

The author would like to acknowledge George Sawaya, MD, Darragh Flynn, MD, Lynn Hansen, NP, and Carolyn Muir, NP, for helpful comments on earlier versions of this manuscript. Dr. Walsh is a recipient of a Cancer Control Career Development Award from the American Cancer Society. She also thanks Dr. Ernest Rosenbaum and the Howard Dobbs Fund of Mount Zion Health Systems for generous grant support.

REFERENCES

1. Christopherson WM, Parker JE. Relation of cervical cancer to early marriage and childbearing. N Engl J Med 1965; 273:235–239

2. Winkelstein WJ. Smoking and cervical cancer—current status: a review. Am J Epidemiol 1990; 131:945–957

3. Rotkin ID. Epidemiology of cancer of the cervix: sexual characteristics of a cervical cancer population. Am J Public Health Nations Health 1967; 57:815–829

4. Kessler II. Human cervical cancer as a venereal disease. Cancer Res 1976; 36:783–791

5. U.S. Preventive Services Task Force. Report of the U.S. Preventive Services Task Force. Guide to Clinical Preventive Services. 2nd edition. Alexandria. VA: International Medical Publishing; 1996

6. American Cancer Society. Guidelines for the cancer-related checkup: an update. Atlanta: American Cancer Society; 1993

7. Van Wijngaarden WJ, Duncan ID. Rationale for stopping cervical screening in women over age 50. BMJ 1993; 306:967–971

8. Mandelblatt J, Traxler M, Lakin P, Kanetsky P, Kao R. Mammography and Papanicolaou smear use by elderly poor black women. Harlem Study Team. J Am Geriatr Soc 1992; 40:1001–1007

9. Mandelblatt J, Gopaul I, Wistreich M. Gynecologic care of elderly women: another look at Papanicolaou smear testing. JAMA 1986; 256:367–371

10. Yu S, Miller AB, Sherman GJ. Optimizing the age, number of of tests and test interval for cervical cancer screening in Canada. J Epidemiol Commun Health 1982; 36:1–10

11. National Cancer Institute. National Health Interview Survey Supplement on Cancer Control. Bethesda, MD: National Center for Health Statistics; 1989

12. Kurman RJ, Henson DE, Herbst AL, Noller KL, Schiffman MH for the 1992 National Cancer Institute Workshop. Interim guidelines for management of abnormal cervical cytology. JAMA 1994; 271:1866–1869

13. Ostor AG. Natural history of cervical intraepithelial neoplasia: a critical review. Int J Gynecol Pathol 1993; 12:186–192

14. Richart RM, Wright TCJ. Controversies in the management of low-grade cervical intraepithelial neoplasia. Cancer 1993; 71:1413–1421

15. Mareck DG, Woolard DG. ViraPap: can it help to reduce the need for colposcopy? Fam Pract Res J 1991; 11:405–413

16. Bauer HM, Ting Y, Greer CE, Chambers JC, Tashiro CJ, Chimera J, et al. Genital human papillomavirus infection in female university students as determined by a PCR-based method. JAMA 1991; 265:472–477

17. Meyer MP, Carbonell RI, Mauser NA, Kanbour AI, Amortegui AJ. Detection of human papillomavirus in cervical swab samples by ViraPap and in cervical biopsy specimens by in situ hybridization. Am J Clin Pathol 1993; 100:12–17

18. Kiviat NB, Koutsky LA, Critchlow CW, Galloway DA, Vernon DA, Peterson ML, et al. Comparison of Southern transfer hybridization and dot filter hybridization for detection of human papillomavirus infection with types 6, 11, 16, 18, 31, 33 and 35. Am J Clin Pathol 1990; 94:561–565

19. Syrjanen S, Syrjanen K, Mantyjarvi R, Parkkinen S, Vayrynen M, Saarikoski S, Castren O. Human papillomavirus (HPV) DNA sequences demonstrated by in situ DNA hybridization in serial paraffin-embedded cervical biopsies. Arch Gynecol 1986; 239:39–48

20. Caussy D, Marrett LD, Worth AJ, McBride M, Rawls WE. Human papillomavirus and cervical intraepithelial neoplasia in women who subsequently had invasive cancer. Can Med Assoc J 1990; 142:311–317

21. Weaver MG, Abdul-Karim, FW, Dale G, Sorensen K, et al. Outcome in mild and moderate cervical dysplasias related to the presence of specific human papillomavirus types. Mod Pathol 1990; 35:697–703

22. Rando RF, Sedlacek TV, Hunt J, Jenson AB, Kurman RY, Lancaster WD. Verrucous carcinoma of the vulva associated with an unusual type 6 human papillomavirus. Obstet Gynecol 1986; 67:70S–75S

23. Koutsky LA, Galloway DA, Holmes KK. Epidemiology of genital human papillomavirus infection. Epidemiol Rev 1988; 10:122–163

24. Wright TC, Richart R. Role of human papillomavirus in the pathogenesis of genital tract warts and cancer. Gynecol Oncol 1990; 37:151–164

25. Wilczynski SP, Bergen S, Walker J, Liao WY, Pearlman LF. Human papillomaviruses and cervical cancer. Hum Pathol 1988; 19:697–704

26. Tase T, Okagaki T, Clark BA, Manias DA, Ostrow RS, Twiggs LB, Faras AJ. Human papillomavirus types and localization in adenocarcinoma and adenosquamous carcinoma of the uterine cervix: a study by in situ DNA hybridization. Cancer Res 1988; 48:993–998

27. Reid R, Greenberg M, Jenson AB, et al. Sexually transmitted papillomaviral infections. I. The anatomic distribution and pathologic grade of neoplastic lesions associated with different viral types. Am J Obstet Gynecol 1987; 156:212–222

28. Goff BA, Muntz HG, Bell DA, Wertheim I, Rice LW. Human papillomavirus typing in patients with Papanicolaou smears showing squamous atypia. Gynecol Oncol 1993; 48:384–388

29. Bollen LJ, Tjong-A-Hung SP, van der Velden J, Brouwer K, Mol BW, ten Kate FJ, ter Schegget J. Human papillomavirus deoxyribonucleic acid detection in mildly or moderately dysplastic smears: a possible method for selecting patients for colposcopy. Am J Obstet Gynecol 1997; 177:548–553

30. Linder J, Zahniser D. The ThinPrep Pap test. A review of clinical studies. Acta Cytologica 1997; 41:30–38

31. Cytyc Corp. PMA material received from company. Cytyc Corporation, Boxborough, MA, 1996

32. Hutchinson ML, Cassin CM, Bal HG. The efficacy of an automated preparation device for cervical cytology. Am J Clin Pathol 1991; 96:300–305

33. Sheets EE, Constantine NM, Dinisco S, et al. Colposcopically directed biopsies provide a basis for comparing the accuracy of ThinPrep and Papanicolaou smears. J Gynecol Tech 1995; 1:27–34

34. Hutchinson ML, Agarwal P, Denault T, Berger B, Cibas ES. A new look at cervical cytology: ThinPrep multicenter trial results. Acta Cytol 1992; 36:499–504

35. Linder J. Automation of the papanicolaou smear: a technology assessment perspective. Arch Pathol Lab Med 1997; 121:282–286

36. NeoPath Inc. Executive Summary of PMA P950009. Material from manufacturer, and reports of clinical evaluation and sensitivity studies. NeoPath, Inc., Bellevue, WA, 1995

37. Koss LG. Cervical (Pap) smear: new directions. Cancer 1993; 71(4 suppl):1406–1412

38. Ryan MR, Stastny JF, Remmers R, Pedigo MA, Cahill LA, Frable WJ. PAPNET-directed rescreening of cervicovaginal smears: a study of 101 cases of atypical squamous cells of undetermined significance. Anat Pathol 1996; 106:711–718

39. Montz FJ, Bradley JM, Fowler JM, Nguyen L. Natural history of the minimally abnormal Papanicolaou smear. Obstet Gynecol 1992; 80:385–388

40. Patten SFJ. Diagnostic cytopathology of the uterine cervix. In Wied GL, (Ed): Monographs in Clinical Cytology, 2nd edition. Basel, Switzerland: S Karger AG; 1978, pp 92–113

41. Nasiell K, Roger V, Nasiell M. Behavior of mild cervical dysplasias during long term follow-up. Obstet Gynecol 1986; 67:665–669

42. Brown M, Phillips G. Management of the mildly abnormal Pap smears: a conservative approach. Gynecol Oncol 1985; 22:149–153

43. Carmichael JA, Maskens PD. Cervical intraepithelial neoplasia: examination, treatments and follow-up review. Obstet Gynecol Surg 1985; 40:545–552

44. Miller AB, Anderson G, Brisson J, et al. Report of a national workshop on screening for cancer of the cervix. Can Med Assoc J 1991; 145:1301–1325

45. Vooijs GP. De averisering bij de afwjkende bevindingen van cytologischonderzoek van de cervix uteri. NTvG 1987; 131:1662–1663

46. Haffenden DK, Bigrigg A, Codling BW, Read MD. Pregnancy following large loop excision of the transformation zone. Br J Obstet Gynaecol 1993; 100:1059–1060

47. Ridgley R, Hernandez E, Cruz C, Miyazawa K. Abnormal Papanicolau smears after earlier smears with atypical squamous cells. J Reprod Med 1988; 33:285–288

48. Goff BA, Atansoff P, Brown E, Muntz HG, Bell DA, Rice LW. Endocervical glandular atypia in Papanicolaou smears. Obstet Gynecol 1992; 79:101–104

49. Schwartz SM, Weiss NS. Increased incidence of adenocarcinoma of the cervix in young women in the United States. Am J Epidemiol 1986; 124:1045–1049

50. Peters RK, Chao A, Mack TM, Thomas D, Bernstein L, Henderson BE. Increased frequency of adenocarcinoma of the uterine cervix in young women in Los Angeles County. J Natl Cancer Inst 1986; 76:423–428

51. Parazzini F, La Vecchia C. Epidemiology of adenocarcinoma of the cervix. Gynecol Oncol 1990; 39:40–46

52. Duska LR, Flynn CF, Chen A, Whall-Strojwas D, Goodman A. Clinical evaluation of atypical glandular cells of undetermined significance on cervical cytology. Obstet Gynecol 1998; 91:278–282

53. Zweizig S, Noller K, Reale F, Collis S, Resseguie L. Neoplasia associated with atypical glandular cells of undetermined significance on cervical cytology. Gynecol Oncol 1997; 65:314–318

54. American College of Obstetrics and Gynecology. Cervical cytology: evaluation and management of abnormalities. ACOG technical bulletin no. 183. Washington, DC: ACOG; 1993, pp 1–7

55. Kivlahan C, Ingram E. Papanicolaou smears without endocervical cells: are they inadequate? Acta Cytologica 1986; 30:258–260

56. Mitchell H, Medley G. Longitudinal study of women with negative cervical smears according to endocervical status. Lancet 1991; 337:265–267

57. Joseph MG, Cragg F, Wright VC, Kontozoglou TE, Downing P, Marks FR. Cyto-histological correlates in a colposcopic clinic: a 1-year prospective study. Diag Cytopathol 1991; 7:477–481

58. Fetters MD, Fischer G, Reed BD. Effectiveness of vaginal Papinicolau smear screening after total hysterectomy for benign disease. JAMA 1996; 275:940–947

59. Pearce KF, Haefner HK, Sariwar SF, Nolan TE. Cytopathological findings on vaginal Papanicolaou smears after hysterectomy for benign gynecologic disease. N Engl J Med 1996; 335:1559–1562

60. Fischer G, Fetters MD, Ruffin M. Vaginal smears after hysterectomy. J Fam Pract 1995; 41:16

Medical Informatics

Medicine and the Internet

HARUKO AKATSU, MD; *and* JAMES KUFFNER, MS, *Stanford, California*

Practicing physicians are frequently overwhelmed by the amount of new medical information. The internet is increasingly becoming an important vehicle for accessing that information with a variety of online resources for medical professionals. In its current state, however, the internet abounds with misleading information, making it difficult to sort out what is both meaningful and accurate from among the thousands of electronic documents. In this article, we list medical web sites that we have found to be useful, accurate, and easy to navigate. We also give an overview of the internet and World Wide Web to provide a starting point for novice users, and we briefly discuss how internet policy relates to medical practice.

(Akatsu H, Kuffner J. Medicine and the internet. West J Med 1998; 169:311–317)

Each day, the number of online medicine-related documents grows, and many can be accessed via the internet. This powerful free-flow of information holds the promise of improving the standard of care in many ways. Important hazards, however, accompany this rapidly growing body of largely unorganized information. The lack of standards and peer review for documents published on the internet poses significant risks for those seeking to use medical information found online. Medical professionals need to become acquainted with internet technology to exploit its powers while remaining fully aware of its limitations and dangers.

The Internet

The internet is a highly complex network that interconnects millions of computers around the world. It allows the rapid transfer of information from one computer to another. This information can take the form of textual data, graphic images, digitized sound and video, and other electronic data.

The internet originated in 1969 as a project by the Defense Department to connect geographically dispersed U.S. military computers, various government laboratories, and contractors. The internet was demilitarized in 1983, when the defense functions were transferred to another network. The internet's current structure is largely the work of the National Science Foundation which, recognizing the value of the internet to the scientific community, devoted tremendous resources to it. In 1995, large telecommunications companies formed the long-distance networks, which became the backbone of the internet as it went global.[1] Today, millions of computers around the world are connected to the internet, and the number grows exponentially each year.

There are many different methods of connecting to the internet. If one has a personal computer at home or at a private office, the easiest way to connect is through a modem via an *internet service provider (ISP)* (for a list of popular ISPs, see Table 1). An ISP connection method works over a standard telephone line and involves simply dialing the ISP's telephone number. If one is affiliated with a university, an e-mail account and telephone dial-up web access are typically provided free of charge, eliminating the need for an ISP. Although simple and convenient, connecting via a modem generally provides the slowest connection in terms of *data transfer rates*. Higher connection speeds can be obtained at greater cost. Examples include *dual modems* or dedicated *ISDN lines*. New technologies for connecting include *cable modems*, *XDSL* (digital subscriber) *lines*, and *satellite link-ups*. These technologies are becoming more affordable every day and offer greatly increased data transfer rates.

Once connected, one can use the internet in many different ways, including e-mail, newsgroups, listservs, and the World Wide Web (WWW or the web).

E-mail may be sent between any users with *e-mail accounts*. By simply typing a document (letter, memo, question) onto a computer that is connected to the internet, one can send and deliver the message almost instantaneously. E-mail accounts and services are available through universities, institutions, or ISPs. An e-mail account is specified by an *e-mail address*, which is composed of two parts: the *username* and the *domain*, usually separated by the character @. The domain identifies the computer system where the mailbox is located,

From the Department of Medicine, Stanford University School of Medicine (Dr Akatsu), and the Department of Computer Science, Stanford University School of Engineering, Stanford, California.

Reprint requests to Haruko Akatsu, MD, Stanford University School of Medicine, Division of Endocrinology, Room S005, Stanford, CA 94305-510.

ABBREVIATIONS USED IN TEXT

FAQ = frequently asked questions
HTML = hypertext markup language
ISP = internet service provider
URL = uniform resource locator
WWW = World Wide Web

and the username is an unique sequence of letters or numbers identifying a particular user at the given domain (often the first name, last name, or initials of the user). Domains ending with the suffix ".edu" indicate U.S. educational institutions, the suffixes ".gov" or ".mil" correspond to U.S. government or military agencies, ".com" indicates private commercial institutions, and ".org" indicates noncommercial public or private organizations. For example, an e-mail address such as "haruko@leland.stanford.edu" means that the user goes by the username "haruko" and that the e-mailbox is located at Stanford University. Addresses outside the U.S. usually have a domain ending in a country code suffix, such as ".jp" for Japan or ".nz" for New Zealand.

Using e-mail messages as a basis, an internet *newsgroup* acts like an international bulletin board service. Users anywhere in the world can post messages (or *articles*) and respond to messages from other users in discussion groups on more than 10,000 different subjects. The content of these group discussions is generally not moderated or peer-reviewed, but rather serves as an open forum for sharing information and ideas. Most internet users agree that the problem with newsgroups is their very low "signal-to-noise ratio"—one has to wade through a great deal of useless text to stumble across the occasional useful piece of information.[2]

Another variation on pure e-mail messages is a *listserv* system, an e-mail–based newsletter and discussion group. Users *subscribe* (almost invariably without fee) to become a member of a list, so access can be regulated. A central computer contains all of the names and e-mail addresses of the members. When an e-mail message is sent by a member to the listserv central computer, it is *reflected* or sent only to the addresses on the membership list. Subscribing to such a list on a particular subject is one method of improving the low signal-to-noise ratio found on internet newsgroups, since the content is often moderated. Subscribers should be aware, however, of the e-mail *traffic* associated with a particular list. It is not uncommon for some lists to average up to 30–40 messages per day, which can quickly saturate one's e-mail inbox. Unless you are prepared to read your e-mail frequently or use *automatic filters* to sort your e-mail, you should avoid such lists.

One useful word of advice for users new to a particular internet technology (referred to as *newbies* by experienced users) is to search out and read the *FAQ* (the list of frequently asked questions and answers) for a particular newsgroup, listserv, or internet resource. These documents are usually kept up-to-date with answers to the most common questions a new user will have, and often contain important guidelines to follow. Experienced users are easily irritated and can be downright hostile toward users who ignore these guidelines or fail to read the FAQ.[3]

TABLE 1.—*Major Internet Service Providers*

America Online (AOL)	1-800-827-6364
CompuServe	1-800-848-8199
Delphi	1-800-695-4005
Physicians' Online	1-800-332-0009 (no cost for physicians)
Prodigy	1-800-776-3449

The World Wide Web

The core ideas for the web, a subset of the internet, were developed in 1991 at the European High Energy Physics Laboratory.[4] The web is an aggregation of *web documents* containing all sorts of data that are available for anyone to view and *download* (copy from a remote computer to a user's personal computer). A web document is also called a *site* or *page*. A distinguishing characteristic of a web document is the presence of *hypertext links* to other web sites. Selecting a certain word or phrase (usually highlighted in color and underlined) or an image with simple keystrokes or mouse clicks will allow the user instantly to access a linked web document over the internet. The power of the web is this capability to establish links between documents, which could reside on any computer anywhere in the world. The web may be thought of as the largest unified information resource the world has ever known. Through it, one can obtain the latest developments in the treatment of myocardial infarction; hourly stock market numbers; or the current weather in Kyoto, Japan; all without leaving one's own living room.

Anyone with access to an account on a *web server* (a computer that is configured to host web documents) can create one's own web site. One need only use the *hypertext markup language (HTML)*, which is fairly simple to learn, in formatting the document. Thus new web sites are created each day, adding to the many millions of web sites already in existence. At present, there are no real rules regarding the creation and addition of new web sites. This, combined with the current lack of peer-review standards, warrants a healthy skepticism when encountering information on the web. Along with a large number of high-quality resources, there is misleading, inaccurate, incomplete, or out-of-date information floating around on the web. Internet users can have trouble distinguishing the useful from the harmful.[5] The U.S. Food and Drug Administration, which regulates pharmaceutical advertising and promotion in the print and broadcast media, is now considering whether to apply such regulations to the internet.

To access the web, the user needs web *browsing* software. The most widely used browser was created by

TABLE 2.—*General Web Search Systems*

AltaVista	www.altavista.com/
Excite	www.excite.com/
Infoseek	www.infoseek.com/
Lycos	www.lycos.com/
Yahoo	www.yahoo.com/

The keystrokes "http://" should precede all URLs.

Netscape (Mountain View, CA) and is called Navigator, although Internet Explorer by Microsoft (Redmond, WA) is also popular. Once a user is connected to the internet via modem or direct connection, a particular web site can be accessed by simply typing its unique electronic address, the *uniform resource locator (URL)*, or by selecting a highlighted hypertext link on one web page to connect instantly to another web page.

Given the enormous amount of information on the web, finding the desired information becomes a problem.[6] Several sites have been established to categorize the information on the web, much like a database. These sites have *search engines* that allow the user to find information by entering relevant terms. Popular indexes and search tools on the web include Yahoo, AltaVista, Excite, and Lycos (see Table 2 for the URLs for those sites).

Table 3 lists some useful medical web sites for physicians, but it is by no means a complete list. Many new medical web sites are created and added frequently. To create your own personal list of useful medical web sites that fits your needs and style, the best way is to start with some of the search engines listed. Good starting sites for any health-related topics include Doctor's Guide to the Internet, The MED Engine, and Physicians' Online. Users interested in online information as it relates to medicine are referred to the Medical Computing Today web site.

Medical Search Engines

Doctor's Guide to the Internet, a user-friendly, comprehensive search engine, gives the user options to search any topic by *key words*; search recent medical news by subject or date (past 7 days and past month); search new drugs or indications; and view conference schedules by subject, date, or location. It is also connected to a large database of medical resources on the web organized by categories and updated weekly.

The MED Engine gives the user options to be connected to different medical resources by category such as news (medical and general); illness and disease; publications (journals and books); associations, organizations, and institutions; hospital information; employment; office resources; medical reference; educational resources; and general reference (weather, street maps, stock market). It is an excellent, easy-to-use site to start accessing online medical resources.

Physicians' Online (POL), launched in 1994, is designed for physicians and physicians-in-training. To access the site, a user needs to register (free). Physicians' Online has unique features that cannot be found with the above search engines:

1. A rated listing (called the WebGuide) of medical sites on the web categorized by medical specialty or type of site. Each site is rated on a scale of 1 to 5 (1 = poor and 5 = excellent) for clinical relevance, content, ease of use, update frequency, and graphic intensity. Users can constantly grade each site by submitting an online evaluation. The WebGuide also lists whether registration is required for a site. Sites that score an overall rating of 4 or above are given the "POL Physician Approved" seal.
2. Physician-only clinical and general discussion opportunities on various medical topics.
3. Clinical quizzes and surveys for members to participate in and view the results.

MEDLINE

One can search MEDLINE free on the web. Fast and easy-to-use free medline sites include NCBI PubMed MEDLINE, Medscape MEDLINE, Health World MEDLINE, and Physicians' Online MEDLINE. One can find many more free MEDLINE sites by checking Dr Felix's Free MEDLINE homepage, a site that summarizes each database's coverage, frequency of update, registration requirements, usage restrictions, etc.

Medical Associations, Journals, and Reference Texts

Many medical associations and organizations have their own home pages where one can obtain information on conference schedules, participate in discussion groups, and obtain the latest developments in the field. Many medical journals, including *New England Journal of Medicine, Archives of Internal Medicine, Journal of the American Medical Association, Annals of Internal Medicine, The Lancet*, and *British Medical Journal* have tables of contents and each article's abstract available online for free. Some journals have additional online features; for instance, *New England Journal of Medicine* has a collection of full texts of recent articles related to a specific topic (such as breast cancer) available to internet users. On a web site called WebMedLit, which tracks 20–23 major medical journals' latest issues, one can search the latest articles by topic instead of going to individual sites for each journal.

Reviewing human anatomy is now easy online. The NPAC Visible Human Viewer from Northeast Parallel Architectures Center, Syracuse University, allows the user to view high-resolution images of two-dimensional slices (axial, sagittal, and coronal) of a human body, using image data taken from the National Library of Medicine's Visible Human Project. The program is easy to use and the user can simply select the type and the location of a slice by clicking on the image. Another site, Three Dimensional Medical Reconstruction, provided by General Electric Research and Development, allows the user to view three-dimensional images of several parts of the body including the skull, brain, heart, lung,

TABLE 3.—*Useful Web Sites for Physicians*

Good sites to find information on health related topics	
www.pslgroup.com/docguide.htm	Doctor's Guide to the Internet
www.fastsearch.com/med/	The MED Engine
www.pol.net/	Physicians' Online
Other sites to find information on health related topics	
www.jr2.ox.ac.uk/Bandolier/	Bandolier, evidence-based health care
www.centerwatch.com/	CenterWatch Clinical Trials Listing Service
www.med-library.com/medlibrary/	Jonathan Tward's Multimedia Medical Reference Library
www.medmatrix.org/	Medical Matrix
www.medscape.com/	Medscape
www.medsite.com/	Medsite
www.gen.emory.edu/medweb/	MedWeb: Biomedical Internet Resources
www.nlm.nih.gov/	U.S. National Library of Medicine
wwwindex.nlm.nih.gov/index/	Search for information at the National Library of Medicine
www.gretmar.com/webdoctor/home.html	WebDoctor Home Page
www.yahoo.com/Health/Medicine/	Yahoo's Medical Links
medicalcomputingtoday.com/	Medical Computing Today
Free MEDLINE on the internet	
www.healthy.net/Library/search/medline.htm	HealthWorld MEDLINE Search
www.medscape.com/misc/formmedlineInfLive.html	Medscape MEDLINE (free registration required)
www4.ncbi.nlm.nih.gov/PubMed/	PubMed
How to search free MEDLINE sites	
www.docnet.org.uk/drfelix/	Dr Felix's Free MEDLINE Page
Medical Associations, Organizations, and Societies	
www.aaaai.org/	American Academy of Allergy, Asthma and Immunology
www.aafp.org/	American Academy of Family Physicians
www.eyenet.org/	American Academy of Ophthalmology
www.aaos.org/	American Academy of Orthopaedic Surgeons
www.entnet.org/	American Academy of Otolaryngology—Head and Neck Surgery
www.aap.org/	American Academy of Pediatrics
www.aapmr.org/	American Academy of Physical Medicine & Rehabilitation
www.aace.com/	American Association of Clinical Endocrinologists
www.scienceXchange.com/aai/	American Association of Immunologists
www.cancer.org/	American Cancer Society
allergy.mcg.edu/	American College of Allergy, Asthma & Immunology
www.acc.org/	American College of Cardiology
www.chestnet.org/	American College of Chest Physicians
www.acg.gi.org/	American College of Gastroenterology
www.acog.com/	American College of Obstetricians and Gynecologists
www.acponline.org/	American College of Physicians–American Society of Internal Medicine
www.facs.org/	American College of Surgeons
www.diabetes.org/	American Diabetes Association
www.gastro.org/	American Gastroenterological Association
www.amhrt.org/	American Heart Association
www.ahmaholistic.com/	American Holistic Medical Association
www.lungusa.org/	American Lung Association
www.ama-assn.org/	American Medical Association
www.psych.org/	American Psychiatric Association
www.faseb.org/ain/	American Society for Nutritional Sciences
www.asco.org/	American Society of Clinical Oncology
www.hematology.org/	American Society of Hematology
www.ash-us.org/	American Society of Hypertension
www.asmusa.org/asm.htm	American Society for Microbiology

Continued on following page —

— TABLE 3 continued

www.thyroid.org/	American Thyroid Association
www.arthritis.org/	Arthritis Foundation
www.aep.org/	Association of Emergency Physicians
www.cdc.gov/	Centers for Disease Control and Prevention
www.endo-society.org/	Endocrine Society
www.fda.gov/	U.S. Food and Drug Administration
www.nari-assn.com/	National Association of Residents and Interns
www.nbme.org/	National Board of Medical Examiners
www.nci.nih.gov/	National Cancer Institute
www.nih.gov/	National Institutes of Health
www.stroke.org/	National Stroke Association
www.endocrinology.org/	Society for Endocrinology
www.census.gov/	U.S. Census Bureau
www.who.int/	World Health Organization
www.niddk.nih.gov/	The National Institute of Diabetes and Digestive and Kidney Diseases
Web site listing the latest medical journal articles	
www.webmedlit.com/	WebMedLit
Publishers of medical journals on the internet	
www.ama-assn.org/public/journals/	American Medical Association Specialty Journals
www.cjp.com/	Carden Jennings Publishing
www.elsevier.com/	Elsevier Science Publications
www.com/	Lippincott Williams & Wilkins
www.mosby.com/	Mosby Health Professionals Center
www.munksgaard.dk/	Munksgaard
www.springer-ny.com/	Springer-Verlag New York
Medical journals on the internet	
www.munksgaard.dk/allergy/	Allergy
www.sph.jhu.edu/pubs/jepi/	American Journal of Epidemiology
www-east.elsevier.com/ajg/	American Journal of Gastroenterology
www-east.elsevier.com/ajpm/	American Journal of Preventive Medicine
www.appi.org/ajp/	The American Journal of Psychiatry
www.acponline.org/journals/annals/annaltoc.htm?wni	Annals of Internal Medicine
www.acponline.org/journals/journals.htm	ACP Journal Club
(enter through www.mosby.com/):	
American Journal of Obstetrics and Gynecology	
Annals of Emergency Medicine	
Journal of Allergy & Clinical Immunology	
Journal of the American Academy of Dermatology	
Otolaryngology—Head and Neck Surgery	
(enter through www.ama-assn.org/public/journals/):	
Archives of Family Medicine	
Archives of Internal Medicine	
Archives of Neurology	
www.bloodjournal.org/	Blood
www.bmj.com/bmj/	British Medical Journal
journals.chestnet.org/chest/	Chest
www.apnet.com.:80/www/journal/ii.htm	Clinical Immunology and Immunopathology
www.at-home.com/amhrt/CIRC/	Circulation
www.diabetes.org/diabetes/	Diabetes
www.diabetes.org/diabetescare/	Diabetes Care
journals.endocrinology.org/	Endocrinology
www.gastrojournal.org/	Gastroenterology
www.modernmedicine.com/geri/	Geriatrics

Continued on following page —

—TABLE 3 continued

www.ama-assn.org/public/journals/jama/	JAMA
www.jci.org/	The Journal of Clinical Investigation
www.jcojournal.org/	Journal of Clinical Oncology
www.thelancet.com/	The Lancet
www.cdc.gov/epo/mmwr/mmwr.html	Morbidity and Mortality Weekly Report
www.nejm.org/	The New England Journal of Medicine
www.wjmed.com/	The Western Journal of Medicine
Pharmacology	
pharminfo.com/drg_mnu.html	Drug Information Database
Anatomy	
www.npac.syr.edu/projects/vishuman/VisibleHuman.html	The NPAC Visible Human Viewer
www.crd.ge.com/esl/cgsp/projects/medical/	Three Dimensional Medical Reconstruction

The keystrokes "http://" should precede all URLs. All URL addresses were checked for accuracy at the time of publication; however, because of the ever-changing nature of the internet, some sites may have moved.

colon, and torso. The images are derived from slice data from a variety of medical image modalities such as magnetic resonance imaging and computerized tomography.

Disease-Specific Sites

Numerous disease-specific reference sites can be found on the web. Some are created by national organizations (such as Introduction to Crohn's Disease by the National Institutes of Health and CDC National AIDS Clearinghouse by the Centers for Disease Control and Prevention). Others are created by individual universities, medical centers, departments, or divisions (such as Cardiology Compass by Washington University School of Medicine, Section of Medical Informatics, and Thyroid Home Page by Santa Monica Thyroid Diagnostic Center).

Other sites were created by individuals: patients, families of patients, physicians, and other health-care providers. Some examples include Sinusitis: A Treatment Plan That Works for Asthma and Allergies Too by Dr. Tichenor in New York; The Nephron Information Center by Dr. Fadem in Texas; The Tourette Syndrome Home Page by a 22-year-old patient with Tourette syndrome; and Alzheimer's Disease by a social worker who specializes in the care of Alzheimer's and related dementia. It is almost impossible to tell who has created or is maintaining these sites just by looking at their titles.[7] Some of these pages do clearly say who or what organization is responsible for the information given, but others are less clear about authorship. The web is also abundant with different patient support sites, individual hospital and medical school home pages, and individual patient and physician home pages. Again, anyone can create a web page on any topic, and there is currently no review system for the information published online. Users need to maintain a healthy skepticism when accessing any of these web sites.

Internet Policy and How It Relates to Medical Practice

There are no real rules or peer-review standards regarding web sites, and there appears to be no reasonable way to control the vast majority of sites with potentially misleading medical information without infringing on free speech.

One workaround is to rely on *master lists*, or web sites containing lists of trusted sites that are maintained by trusted organizations or individuals. Those responsible for creating and maintaining the master list will have critically reviewed many sites on a specific topic and compiled a list of links to those sites that they deem to be both useful and accurate. Examples of such sites include the American Diabetes Association's list of internet resources (http://www.diabetes.org/internetResources.htm) and the National Stroke Association's list of stroke-related sites (http://www.stroke.org/Related_Websites.html). Someone wishing to find trusted information on a particular topic would begin by first looking at master list sites of *prefiltered links*. Unfortunately, there are a number of drawbacks to master lists: new sites are created every day, so unless master lists are frequently updated, they may not always contain links to the best sites or the most recent data. Even worse, due to the dynamic and ever-changing nature of information on the internet, sites that were initially reviewed favorably may alter their content without warning. Unless the maintainers of a master list expend significant effort constantly reviewing and reassessing their information, they may inadvertently find themselves linking to inaccurate or contradictory information. Perhaps the most subtle danger in this regard has to do with the nature of the web itself. Hyperlinks allow one to rapidly jump between sites as one browses and explores information in detail. It is easy to quickly lose track of who is responsible for the information contained on a particular page or how one arrived at that page. A web site reviewed favorably and contained on a master list may itself contain one or more links to unfavorable sites. The web is truly a tangled web indeed.

Silberg et al[8] proposed a set of basic guidelines for information published online, based on principles widely used in traditional print publishing. The aim is to equip the viewers of online information with the ability to rea-

sonably judge the quality and credibility of the content viewed. The guidelines are restated briefly as follows:

Authorship: Authors and contributors, their affiliations, and relevant credentials should be provided.

Attribution: References, sources, and any copyrights for all content should be listed clearly.

Disclosure: Web site "ownership" should be prominently and fully disclosed, including any sponsorship, underwriting, advertising, commercial funding or support, or potential conflicts of interest, which include arrangements for links to other sites to be posted as a result of financial considerations.

Currency: Dates that the content was posted and updated should be indicated.

We applaud guidelines such as these, and hope that more and more web sites will abide by them as a service to the online community.

Privacy and Security

The issues of privacy and security on the internet, which have received much media attention, are of particular relevance as hospitals and physicians contemplate providing internet access to patient data. The potential benefits of such access to the medical community are significant, but the potential risks are of great concern. For a broad, thought-provoking discussion, readers are referred to the article by Jacobson.[9] Below, we touch briefly on the fundamental issues.

Online access to health care information roughly falls into two categories: access to *individual patient data*, such as individual medical charts and records, and access to *generic health care information*, such as epidemiological data. The importance of ensuring privacy and security of individual patient data is obvious. Security on the internet is an extremely complex issue involving cryptography research and its sophisticated software, questions of national security, and the privacy of personal communications. Increasingly sensitive information is being transmitted over the internet every day, including online purchases with credit cards and online banking and stock transactions. It is clear that secure access to patient data must go beyond simple username and password protection schemes, but it will be some time before such access becomes ubiquitous.

The issues of privacy and security are of much less concern when contemplating online access to generic health care information (data that cannot be traced to a single individual). Generic data can be extremely useful for epidemiological studies or quality control. Ensuring the anonymity of such data can be extremely difficult, however, since it may contain subtle but significant threats to patient confidentiality. One example of seemingly innocuous data that contain the potential for abuse are the so-called *scrubbed databases*,[10] databases in which patient identifiers have been removed to preclude identification of individuals. If enough secondary information is available, however, it is possible to uniquely identify individual patients. For example, if there is only one Asian female of a certain age in a specific zip code, this collection of supposedly harmless demographic data will uniquely identify that individual. Furthermore, even if one particular database does not contain enough information to uniquely identify an individual, the *combination* (or *merging*) of that database with other online databases may. One example cited in the literature involved a bank officer who combined a database of cancer patients with an account database in order to call in loans.[10]

Conclusions

Technology will undoubtedly continue to transform the ways in which we communicate and think about medical information. If current trends continue, the practice of medicine in the 21st century will increasingly involve the flow of electronic information over intrahospital or worldwide computer networks.[11] Patients may expect hospitals and private clinics to maintain web sites with information ranging from directions to the office, hours of operation, and emergency phone numbers to professional biographies of the physicians, nurses, and other staff members. Patients may come to their appointments armed with medical information obtained from the internet,[12] expecting physicians to be familiar with the latest research published electronically. In any case, physicians of today should become acquainted with online technology to prepare themselves for the practice of medicine in the future. This includes knowing the positive aspects of the technology as well as its potential dangers and pitfalls. Combined with a healthy skepticism, the internet can be a truly powerful tool for keeping up with the rapid advances in medicine, enabling doctors to provide the best possible care to patients.

REFERENCES

1. Glowniak JV. Medical resources on the internet. Ann Intern Med 1995; 123:123–131

2. Kramer JM, Cath A. Medical resources and the internet. Arch Intern Med 1996; 156:833–842

3. Peters R, Sikorski R. Digital dialogue: sharing information and interests on the internet. JAMA 1997; 277:1258–1260

4. Wang KK, Wong Kee Song LM. The physician and the internet. Mayo Clin Proc 1997; 72:66–71

5. Hersh W. Evidence-based medicine and the internet [editorial]. ACP J Club 1996; A14–A16

6. Peters R, Sikorski R. Navigating to knowledge: tools for finding information on the internet. JAMA 1997; 277:505–506

7. Sonnenberg FA. Health information on the internet. Arch Intern Med 1997; 157:151–152

8. Silberg WM, Lundberg GD, Musacchio RA. Assessing, controlling, and assuring the quality of medical information on the internet. JAMA 1997; 277:1244–1245

9. Jacobson M. AMIA '97: internet access to patient data. Med Computing Today [online edition]. Clinical Computing Dec 1997; http://medicalcomputingtoday.com/index.html

10. Sweeney L. Guaranteeing anonymity when sharing medical data, the Datafly System. Proc 1997 AMIA Ann Fall Symposium. JAMA 1997; 4 (suppl):51–55

11. Kassirer JP. The next transformation in the delivery of health care. N Engl J Med 1995; 332:52–54

12. Widman LE, Tong DA. Requests for medical advice from patients and families to health care providers who publish on the World Wide Web. Arch Intern Med 1997; 157:209–212

Commentary

False Names

NEAL RENDLEMAN, MD, *Portland, Oregon*

A patient's unique, personal name is fundamental in medical relationships. Sometimes, patients may use false names, which obscure family, ethnic, sexual, or billing identities. The means and motivations involved—fraud, concealment, gaining financial or personal advantage, gratifying a psychic need, or changing group assignment—produce a variety of distinct clinical manifestations of false name use. These may be classified as alias, pseudonym, manipulator, fraud, psychotic, amnestic, medical factitioner, and renamed. The identification of falsely named patients enables clinicians to improve care for these types of patients. Individual cases are briefly described and a discussion of naming in society and medicine follows. This preliminary discussion may serve to fuel further refinement.

The name of a patient, basic in most medical contacts as well as in virtually every human interaction,[1] has a number of important attributes. A name indicates membership in families, ethnic groups, and gender classes. A name also provides a distinguishing indicator for filing, billing, and charting. Physicians and the medical system use these properties as a matter of course. Mechanisms by which people change their names by marriage or court action are readily dealt with by this system and by physicians.[2]

There are, however, a collection of syndromes and circumstances in which patients withhold or deny their legal names. In these cases the social, familial, or sexual identity associated with the patient's original name may be the attribute which the patient is trying to deny or obscure. Alternatively the patient may try to manipulate one or another of these attributes to achieve some change in personal identity. The patient may be consciously deceitful or may believe the name given is real in gratification of some psychic purpose. Every experienced clinician can readily recall a series of patients who have used a false name or withheld a name; in 12 years in a homeless health center, I have seen more than 100. Although these syndromes seemingly are heterogeneous, they can be grouped into 8 discrete types. The following brief case histories present these types, discuss some of the implications, and comment on the overarching circumstances of names in the medical relationship. These 8 are not necessarily the same as the John Doe syndrome described in the emergency room literature although there is some overlap.[3]

Alias

A 55-year-old man who had chronic stable angina after a bypass developed unstable angina. After attempts to retrieve old records proved unsuccessful, he reluctantly revealed that he was using an alias supplied by the federal witness protection program. The program did supply records, blinded to name, hospital, and date.

Because this patient had a reasonable fear of death if his true name were revealed, a physician should aid the patient by maintaining confidentiality from all who have no need to know of the existence of the alias. This class includes those whose use of a false name is a result of factors external to the medical system. When the system needs to reference data under the old name, ensuing difficulties affect necessary care.

Pseudonym

A 23-year-old woman registering for her first visit as "Mary Smith" had a black eye and multiple bruises on her torso. She spoke openly about her reasons for using a pseudonym: "My boyfriend did this. He said that if I went to a doctor he would do it again twice as bad."

The frightened victim of abuse might use a pseudonym when seeking medical care. A gang member joins this group when a medical institution assigns the patient a pseudonym to reduce the chances of a repeat assault. Physicians need to be alert to patterns of injury, age, or gender in trauma victims likely to use a false name. If the use of a false name is noted in the chart, the victim can later uncover the pseudonym and use the medical records to prosecute the criminals who caused the injury. Also, the use of the false name may lead to misconceptions concerning family and group identity. Because these problems occur frequently and legal issues surround the use of the false name, a body of practice concerning these issues has arisen.[4] An open attitude by clinicians, cooperation with the patient, use of a "John Doe" label or numbered samples, and an "also known

(Rendleman N. False names West J Med 1998; 169:318–321)

From the Old Town Clinic, Good Samaritan Hospital Primary Care Internal Medicine Program, Portland, Oregon.
Reprint requests to Neal Rendleman, MD, 219 W Burnside St, Portland, OR 97209.

as" code on charts and appointment books can facilitate care while leaving open a route for later use of the patient's charts in legal proceedings.

Manipulator

A 50-year-old man who had been cut on the job was given cash by his employer who instructed him to pay for his medical care without revealing his real name lest the employer's insurance rates go up. The patient's refusal to tell what industry he worked in or what might have contaminated his wounds could have compromised his care.

The difficulties in caring for manipulative patients should not be a barrier to achieving necessary objectives. These patients, in seeking to limit the clinician's access to identifying data, may be reluctant to undergo a complete examination, submit samples for testing, or pay for services. The prudent physician should note the use of a false name on the chart, offer an appropriate range of services, and give the patient an opportunity in the future to set aside the false name.

Fraud

A 22-year-old man underwent a complex hospital stay for a new onset of ulcerative colitis. On his 22nd hospital day, a frequent visitor revealed that he had loaned the patient his insurance card, which provided for 21 days of paid hospital care per year. The patient's care may have been altered by the cardholder's past medical records at that hospital.

The fraudulent patient's care is a challenge because the trust inherent in a physician-patient bond may be broken. Fraudulent patients probably are more common than their detection.[5] As our medical system increasingly evolves into a world of haves and have-nots, the financial offices will screen more intensively, thereby increasing detection of fraudulence. Drug seekers and patients with highly stigmatized conditions may practice fraud to conceal their identities or to get access to the system. The physician's ethical code requires that essential care be provided; moreover, physicians should take systemic action so that people with life-threatening illnesses, pain, or contagious conditions do not feel pressed into fraud. The physician must document fraud and cooperate with its prosecution so that the burden of payment is not shifted to honest people.

Psychotic

A 35-year-old man sought care at a homeless health center for an infected foot blister. He recorded his name as an unpronounceable glyph, which was a pair of arcane symbols drawn as a picture. The foot healed with routine care. All the resources of the homeless health center were necessary to establish the new identity and provide him access to housing, disability payments, and medications. He now lives in a secure, clean environment where similar complications have been avoided.

Cases of psychotic patients who obscure their past identities with a new name present many difficulties because medical history, genetic association, and family ties are blocked. Delusions involved with identity are common in psychiatry. Psychotic patients develop medical conditions which require care before their delusions can be removed.[6] The prudent physician should consult and cooperate with a psychiatrist in these cases and work with the courts and families, when they are known, to get substituted judgment to improve compliance.[7] With a realistic and understanding attitude the physician can increase the odds of a good outcome.

Amnestic

A 43-year-old man developed complete amnesia for all the facts of his identity. During a lengthy hospitalization, punctuated by seizures, he was identified as a traveling salesman who, deciding to break his dependency on the bezodiazapams he acquired from multiple physicians, voluntarily terminated his intake. Other causes of amnesia were ruled out.

The amnestic patient may claim no name or can fabricate a name. Amnesia, though relatively rare, has provoked a medical and lay literature out of proportion to its frequency.[8] Differentiated from dementia and delirium, amnesia has an organic cause in most cases. Because these causes vary greatly and are potentially lethal yet treatable, the amnestic patient is an exciting challenge for the clinical team. These patients, anxious to work together with the team, fit into the accepted paradigm of diagnosis and cure.[9] The long-term challenge for the clinician is to aid the patient's reintegration into his or her personality and society.

Medical Factitioner

A 38-year-old man announced his chief complaint, "I need to get my pancreas cut out," at the same homeless health center where he had been diagnosed with pancreatitis 12 years prior. He gave a history of at least 30 hospitalizations in various cities. Attempts to retrieve records revealed that he had used other names elsewhere in the prior two years. When confronted with this, he decompensated and required involuntary psychiatric commitment.

Patients with a mind-body identity discordance who use false names are the obverse of the amnestic patients in that they are a very bad fit with the medical paradigm. Their chief concern is to have a procedure for a diagnosis for which they may have fabricated exam and laboratory findings. Multiple procedures involving multiple organ systems often are completed by an obliging medical system before some clinician perceives the pattern. Some of these patients, having a totally factitious disease, are given a diagnosis of Munchhausen's syndrome.

Because the previously cited patient had found a means through alcohol use to induce organic illness, he does not meet criteria for Munchhausen's, but the patient's peripatetic behavior, his use of a false name, and his

search for an invasive procedure, do fit the pattern.[10] The greatest threat to these patients is that the medical system, seeking to comply with their cry for help, will subject them to invasive procedures, with the attendant complications. If the behavior can be explained to the patient, complications can be avoided. The use of multiple or factitious names can be a valuable clue to the problem. The medical and social ramifications of Munchhausen's are severely disabling and best addressed with psychiatric consultation.[11]

Renamed

A 40-year-old genotypic male, phenotypic female had used a name interchangeable between genders (such as Pat) for many years. She came to her neighborhood homeless health center with the request, "I need more hormones to keep from aging." She had lived for 22 years as a woman, performing as a cross dresser in a skid row nightclub and working in the sex industry. After she was advised not to use female hormones because of elevated liver enzymes, she took three birth control pills a day for the next three weeks, from packages obtained privately. She was taken to the hospital in fulminant hepatic failure and died.

The transsexual is only one type of renamed patient, although the most prominent one. Some patients use two names in two different niches, including people in the community of gender-identity bending who may have a "street name" and continue to use their given name at work and in their families. Some of these people need special care from the medical system as the result of gender-identity changes. The prudent physician will refer patients to clinics with special multi-disciplinary teams trained to care for this rare but complex type.[12] Issues will arise outside the gender change which can impact on any physician. For example, these patients frequently suffer from violence inflicted upon them and end up in the trauma system. Open acceptance of the problems among transgendered people will improve communication and patient care.[13] On the other hand, not all transgendered and renamed people use hormones or surgery.

Discussion

In surveying the diversity and complexity of the phenomenon of patients' use of false names several questions arise. Are 8 classes enough to encompass the different types of false names? Are all these classes necessary to encompass the different types? Is there any utility to identifying these phenomena together as a syndrome? Is there any unifying principle behind these classes?

Given the variables, these classes are both necessary and sufficient. Patients are pursuing different motives, using differing means and achieving various ends as they manipulate the different attributes of personal names. Concealment is a feature of aliases, the Munchhausen's variants, the fraud, and the psychotic. The other four types are open in varying degrees about the use of the pseudonym. For the four conditions which have primary psychiatric or neurologic features, namely the psychotic, the renamed, the amnestic, and the Munchhausen's, the use of the altered name, or namelessness, is inherent in the condition while the other four have factors extrinsic to their conditions which prompt the adoption of the new name. Another categorization of the 8 groups into 2 arises out of the driving motive, gainseeking. The fraud, the renamed, the medical factitioner, and the manipulator seek to gain some medical intervention while the other groups seek some non-medical advantage such as escape or group reassignment. Thus, within 3 choices—concealed or not, inherent or not, and gainseeking or not—there are 8 classes.

Differentiation is required among these categories because the different syndromes call for different responses. To cite only two obvious examples, a prospective sex-change operation would be contraindicated for a patient with Munchhausen's, and a psychotic who believed he was in the witness protection program would require completely different handling than a genuine alias user. The judicial system's interest in detecting the use of aliases and certifying the legal status of name changes is useful merely to call attention to the fact that a variety of different syndromes exist to which the clinician can be alerted. The compilation of false name syndromes with a systematic classification system presented here provides a differential diagnosis of the causes of false-name use. As soon as one of these syndromes is identified, the prudent physician is alerted to search for the presence of false names.

The unifying principle in these seemingly diverse phenomena of patients who use false names in the medical context takes us back to the fundamental purposes of names in human society. The name is the identifier, the badge of allegiance to family and group, and even a surrogate for identity itself. We are given our name at birth, and sometimes take on additional names at crucial junctions in life. We may change our name when we marry or change religious faiths. We respond to our name as a call and sign it on our contracts. Our gravestone is inscribed with our name when we die. We sign it on our contracts. When we lose credibility or damage our reputation we say we have lost it. In a medical context the patient who uses a false name is marked as having a problem in one of these aspects of human society. The clinician must be alert to the possibility of false names and able to manipulate the attributes of names as they relate to patients in order to provide comprehensive care.

REFERENCES

1. Kaplan J, Bernays A. The Language of Names. New York: Simon and Schuster; 1997

2. Trujillo L. Game for a name change? It's easy. The Oregonian. June 30 1997; Sect A1 (col 6)

3. Claps PJ, Berk WA. The John Doe syndrome: diagnosis and outcome of patients unidentified at the time of emergency department admission. Am J Emer Med 1992; 10:217–218

4. Scott CJ, Matricianni RM. Joint commission on accreditation of health care organization standards to improve care for victims of abuse. Maryland Med J 1994; 891–898

5. Farber NJ, Berger NS, Davis EB, Weiner J, Boyer EJ, Ubel PA. Confidentiality and health insurance fraud. Archives Inter Med 1997; 157:501–504

6. Breakey WR, Fischer PJ, Kramer M, Newstadt G, Romanoski AJ, Ross A, et al. Health and mental health problems of homeless men and women in Baltimore. JAMA 1989; 262:1352–1357

7. Gutheil TG. Legal issues in psychiatry, In Kaplan HI, Sador BJ (Eds): Comprehensive Textbook of Psychiatry. 6th ed. Baltimore: Williams and Wilkins; 1995, pp 2755–2762

8. Hodges JR, Warlow CP. The aetiology of transient global amnesia: A case control study of 114 cases with prospective follow-up. Brain 1990; 113:39–57

9. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington DC: APA; 1994, pp 156–263

10. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington DC: APA; 1994, pp 471–475

11. Loizeau E. Semiologie Digestive et Comportment Psychiatrique: un Point de Vue d'Interniste. Revue Medicale de la Suisse Romande. 1994; 114: 1005–1007

12. Devine CJ, Jordan GH, Schlossberg SM. Surgery of the penis and urethra, In Walsh PPC, Retik AB, Staney TA, Vaughan ED (Eds): Campbel's Urology, 6th ed. Philadelphia: Saunders; 1992, pp 3022–3028

13. Becker H, Hartmann U. Geschlechtsidentitatatsstorungen und die Notwendigkeit der klinischen Perspektive. Fortschritten Neuralogie und Psychiatrie 1994; 62:209–305

Correspondence

Physician-Hastened Death: Blessing or Curse?

SOME TIME AGO, I visited the Museum of Tolerance in Los Angeles. I was reminded that the Nazis did not begin by killing Jews, homosexuals, or dissidents. They began by killing those with physical or mental disabilities, first with drugs and then with gas. This program was the physical and psychological preparation for the Holocaust.[1,2] Opposition came mainly from clergy. Sadly, there was no organized opposition from physicians, many of whom were Nazi party members. A program that was the precursor to monstrous evil deserves intense scrutiny, especially if the recent euthanasia movement has dubious aspects.[3,4]

The lead article in your June 1997 issue[5] advises what to do "...if the practice of physician-hastened death becomes legal." Is it proper to advise physicians how to commit a crime, trusting that they will take the advice only if the law is changed? The article suggests that death certificates list the underlying disease as the cause of death, i.e., that they be falsified. If hastening death is laudable, why conceal it?

The article[5] advises that a second opinion be obtained from one expert in palliative care, but not from one expert in the disease in question, or that slides be reviewed by a second pathologist. Thus the diagnosis of a fatal disease need not be confirmed in ways that physicians would demand if *they* were the patients. Mental competence is mentioned, but not psychiatric consultation to confirm mental competence and rule out depression.

The usual criterion of six months of expected life is used.[5] In 20 years of medical-oncology practice, I saw many patients who defied my predictions. Had we "euthanized" them, we never would have discovered our error. A procedure that causes death, but in which errors cannot be detected, frightens me. That it does not frighten some members of ethics committees frightens me more.

Predictions of life expectancy are uncertain.[6,7] In one study,[6] about 55% of cancer patients predicted to live *less than* 12 months lived one year, 15% lived two years, and 3% lived three or more years. These patients had cancers that were confirmed by experienced pathologists and were not amenable to therapy, but about one in five lived notably longer than predicted. Predictions of survival would be even less reliable with more treatable diseases diagnosed less expertly. Had the patients been "euthanized," errors in prediction would not have been detected.

In two decades of practicing and teaching medical oncology in a county hospital, I saw only one possible suicide, and this in a patient who had used drugs before becoming ill and whose overdose may have been accidental. Not once in all this time did a patient ask about assisted suicide or euthanasia. It seems unlikely that my personality and the personalities of the scores of fellows and residents were all so forbidding that no patient dared to mention this subject. A more likely explanation is that our public teaching hospital and clinic provided a setting where cost was much less a factor than elsewhere. This is borne out by the fact that in Britain, where palliative care is free, only one request for euthanasia was received from about 1800 AIDS patients in hospice.[8] Polls show that 40% of Americans would hasten their deaths to avoid being a burden on others, while only 14% would do so to end their own pain.[9] If we cannot do as well as the underfunded British National Health Service, but respond to fear of being a burden by killing the patient, what does that say about us as physicians and human beings?

Physicians are at least as afraid as others of death and disability, as shown by their tendency to rate disabled patients' quality of life lower than patients themselves rate it.[10–12] Physicians' urge to be in control is threatened by death, the final proof that we are not in control. These fears may be projected onto the patients. It then becomes unclear whether we wish to hasten their death in order to relieve their suffering or our own uneasiness.

A good definition of intelligence is the capacity to learn from experience. Have we learned nothing from 2500 years of tradition ("I will give no deadly medicine to anyone if asked, nor suggest any such counsel")? Have we learned nothing from psychiatry about repressed fears and projection? Have we learned nothing from the hospice movement about adequate palliative care? Have we learned nothing from the Netherlands, where more than 1000 patients annually are "euthanized" without their explicit consent, and where psychiatric illness is now an acceptable cause for euthanasia?[13] Have we learned nothing from the Holocaust, the most terrible lesson in history? If so, are we intelligent enough to survive as a profession? Do we deserve to?

DAVID C. STOLINSKY, MD
Room 10-420, 1200 N. State Street
Los Angeles, California 90033

REFERENCES

1. Lifton RJ. The Nazi Doctors—Medical Killing and the Psychology of Genocide. NY, NY: Basic Books; 1986, pp 45–144

2. Gallagher HG. By Trust Betrayed—Patients, Physicians, and the License to Kill in the Third Reich. NY, NY: Henry Holt, 1990

3. Marker R. Deadly Compassion—The Death of Ann Humphry and the Truth About Euthanasia. NY, NY: William Murrow, 1993

4. Smith WJ. Forced Exit—The Slippery Slope from Assisted Suicide to Legalized Murder. NY, NY: Times Books, 1997

5. Heilig S, Brody R, Marcus FS. Physician-hastened death: advisory guidelines for the San Francisco bay area from the Bay Area Network of Ethics Committees. West J Med 1997; 166:370–378

6. Cassileth BR, Lusk EJ, Guerry D. Survival and quality of life among patients receiving unproven as compared with conventional cancer therapy. N Engl J Med 1991; 324:1180–1185

7. Horgan J. Seeking a better way to die. Scientific American 1997 May; 100–105

8. McKeogh M. Physician-assisted suicide and patients with HIV disease. N Engl J Med 1997; 337:56

9. Silvers A. Protecting the innocents—people with disabilities and physician-assisted dying. West J Med 1997; 166:407–409

10. Gerhart KA, Koziol-McClain J, Lowenstein SR, Whiteneck GG. Quality of life following spinal cord injury—knowledge and attitudes of emergency care providers. Ann Emerg Med 1994; 23:807–812

11. Cushman LA, Dijkers MP. Depressed mood in spinal cord injured patients—staff perceptions and patient realities. Arch Phys Med Rehabil 1990; 71:191–196

12. Madorsky JG. Is the slippery slope steeper for persons with disabilities? West J Med 1997; 166:410–411

13. Groenewoud JH, Van der Maas PJ, Van der Wal G. Physician-assisted death in psychiatric practice in the Netherlands. N Engl J Med 1997; 336:1795–1801

Reply to Dr. Stolinsky

DR. STOLINSKY RAISES many complex points, and we can only respond briefly to some of them or risk submitting another lengthy paper. Regarding the Holocaust experience, it seems to us that any moderately dispassionate examination of that terrible time in history reveals that the analogy is of very limited applicability. The Nazis did not slide down any slippery slope; they started in a cesspool at the bottom, with their genocidal ideology in place, and proceeded from there. Does any reasonable person really believe that the American medical profession, or even our political leaders, harbor such horrible hidden goals?

A more careful reading of our article and guidelines should show that we did not "advise physicians how to commit a crime." Nor did we intend to imply that assisted dying is "laudable." Per our harm-reduction perspective, we recognized that assisted dying is a practice which sometimes occurs as an unfortunate but compassionate last resort, regardless of what we or others "advise." Thus we offered, in concert with more than 100 reviewers from ethics committees throughout the San Francisco Bay Area, some procedural safeguards to help ensure that such events would not occur unnecessarily. And if the guidelines were followed, with the recommended consults and committee review, a physician could hardly be accused of "concealing" the practice. He or she could be accused, however, of trying to keep legal authorities out of the details of clinical practice—a general goal many if not most physicians probably share.

Regarding confirmation of terminal status, assessment of mental state, and predictions of life expectancy, these details were indeed widely—and sometimes heatedly—debated in the process of developing the guidelines. We admit that no such policies or guidelines are perfect. Our group attempted in each case to reach as much of a consensus on these details as possible and to decide by majority vote where consensus was unobtainable. Those who object that no safeguards will be sufficient have less faith in the competency and ethical standards of the average physician (and consultants) than our group. And, we must add, to insist on "perfect" policy is the same as insisting on none.

As for the problem of the cost of medical care and the lack of insurance coverage for it, we are in full agreement with Dr. Stolinsky that this is a problem which represents a great national failure. But we differ in feeling that it is unjustifiable to hold today's patients hostage to that societal failing. While we continue to advocate universal access to health care, in the meantime we must also address the needs of those few patients whose suffering is intolerable to them.

As Dr. Stolinsky observes, most physicians are indeed as fearful and conflicted about death as anyone else. But we believe that, rather than hastening death to relieve their own "uneasiness," physicians currently are more likely to prolong a patient's life by any means possible, even if that entails ignoring advance directives. Unfortunately, widespread experience and published research support that perspective.

Finally, we differ with Dr. Stolinsky's selective reading of literature on the Netherlands' experience, and with his implicit interpretation of the Hippocratic Oath as having an ironclad impact on actual clinical practice. By strict interpretation of that Oath, the widespread use of opiates, and not only in the "terminal sedative" manner now explicitly noted as acceptable by the AMA and the Supreme Court, would be proscribed as the giving of a "deadly medicine." In any event, it can be observed that most people who invoke Hippocrates do so selectively.

The most positive side effect of the assisted dying debate to date has been a focus on improving many aspects of palliative and other end-of-life care. That focus is overdue and must be supported. Still, there is much evidence that some patients do in fact request a hastened death, including in settings where financial considerations are not an issue. Since some physicians apparently do hasten death in some manner in those few cases where it seems an appropriate, if tragic, last resort, we felt that some guidelines should be offered for those who do choose to act in accordance with their own professional and personal standards of medicine and compassion. "Tolerance" is indeed a central part of our perspective. None of us know how our own final weeks and days will unfold, and it seems unwise to arbitrarily limit our options at the time of this most critical life passage.

STEVE HEILIG, MPH
Bay Area Network of Ethics Committees
San Francisco Medical Society

ROBERT BRODY, MD
San Francisco General Hospital

Lessons From the Practice

A New Perspective on the Gatekeeper Role

JOAN E. RUBINSTEIN, MD

This is the story of how I got authorization for my patient to see the specialists at U.C. San Francisco.

About three years ago, Mrs. B. had an episode of angioedema while recovering from a surgical procedure. She did well for several months, then had another episode after starting an ACE-inhibitor for newly diagnosed hypertension. The medication was changed, but over the next two years episodes of angioedema became more frequent and also more severe, resulting in increasingly more frequent visits to our local emergency room. We went through the usual diagnostic and therapeutic maneuvers: physicals, histories, diaries, special diets, and follow-up of even the most trivial-seeming symptoms. I referred Mrs. B. to a respected local allergist, who was equally unsuccessful at identifying a specific trigger or devising effective prophylaxis.

A routine developed. Mrs. B. would develop swelling of the face and tongue, self-inject with epinephrine, then present to the emergency room in severe distress. She would stay for several hours, receiving more adrenergic agents, antihistamines, steroids, H2 blockers, and whatever other nostrums our emergency department could devise, and after a suitable response she would be discharged with instructions to contact me for follow-up within a few days. I began to find these visits an embarrassment. Medically, I had run out of magic bullets, and so had my local consultant. Mrs. B. and I would chat about our families, I would express my sympathy, and she would go merrily if somewhat nervously on her way. Both of us waited for the other shoe to drop.

It was time for drastic measures. I mustered all the appropriate medical records and asked my referral secretary to contact the patient's health plan for authorization to send the patient to the nearest university allergy service. We included as many alarming words as we could in our request, words such as "life-threatening," that I hoped would get the attention of the health plan administrators. I faxed copies of all of the tests and consultations. Maybe I should have pointed out that Mrs. B.'s emergency room bill was already in the thousands of dollars. In any case, I got back a faxed denial, with the statement that the patient could be seen by a local allergist.

Things were quiet for about a month. Then in my mailbox at the hospital was yet another illegible emergency department report and, two days later, there was Mrs. B. in the office. Enough is enough, said I; the primary care physician needs to rattle someone's cage. I called the health plan myself, and, after wending my way through two operators and two voice mail systems, I was connected to the medical director's answering machine.

Imagine my delight when a fax arrived the next day indicating my request had been approved. I gave myself a pat on the back and decided that what everyone said was true—the doctor just had to get on the phone herself and make a little noise. Mrs. B. chanced to come by the office with a plate of cookies and I excitedly explained that we had been given authorization to send her to the university.

She looked genuinely pleased. "You know," she said, "I just heard from my son. He works in Washington as a chef for the President. He was so worried about me that he was telling someone at work about my problem, and they said, 'Donna Shalala is going to hear about this! What's the name of that HMO? Who is that medical director?'"

Yup, assertiveness from the gatekeeper—that's what makes this system run.

(Rubinstein JE: A New Perspective on the Gatekeeper Role. West J Med 1998; 169:324)

Dr. Rubinstein is in private practice in Fowler, California.

Reprint requests to Joan E. Rubinstein, MD, 9451 S. Claremont, Fowler, California, 93625.

Poem

* * *

Mother and Child

(Central Park, summer 1996)

In the midst of chemotherapy,
resistance is the big issue: my mother has lost hers,

so the doctors tell us to be careful of crowds,
children, coughs and sneezes. *No fresh vegetables.*
No restaurant foods, they say. *But hugs are OK,*
and even kisses on the cheek. I believe them.

My older brother has a different idea.
He thinks we can do more,
that we can keep her
germ-free. So he asks me not to use
her bathroom, her sink, and especially not
to get in bed with her.

I remember his warnings as I find a place
to sit, here in Central Park, and watch tiny beetles
crawl near my shorts, then burrow into the thick bark of a trunk,
seeking a home. My belly settles into a cross-legged lap,
and everything rearranges itself once more.

Limbs nudge and kick inside me, push against
stomach, pelvis, ribs. I lean into the trunk
as the baby finds her way around me. She sleeps,
turns, sleeps a little longer. And because sleep comes
hard and slowly for me now, I broke

my brother's rules last night, climbed into bed
with Mother just seconds after she whispered the offer.
I settled into one position, then another, thinking,
I know so little about this child.

I could smell what the doctors warned us about: the preservatives
which kept Mother's bone marrow intact before the transplants.
I called it *sweet* as it soothed me to sleep,
and I imagined her growing stronger from inside.

I want my child, still building her own blood,
to sleep close to her grandmother, to hear another heart
beating through linen sheets.

When I rose to leave the room, I was not
thinking of germs, illness, resistance. I thought only
of our three bodies, while mine, awkward,
off-balance, tried to slip gently from the mattress,
as mother and child slept on.

Kate Reavey
Sequim, Washington

Classified Advertisements

The rate for each insertion is **$1.50 per word, with a 30 word ($45) minimum**. Confidential box number charge: $10 each month.
A word is defined as one or more letters bounded by spaces. The following gives some examples:

Linda H. Clever, MD	= 4 words	allergy/immunology	= 1 word
Send CV	= 2 words	Sacramento, CA 95817	= 3 words
A	= 1 word	804-979-8034	= 1 word
February 22, 1997	= 3 words		

Classified display rate $70 per inch. Maximum sizes: 1 column by 5" or 2 columns by 2" (2-1/8" per column). Larger classified ad space by special arrangements.
Copy for classified advertisements should be received not later than **first of the month preceding issue. All copy must be typed or printed.** Classified advertisers using Box Numbers forbid the disclosure of their identity; your inquiries in writing will be forwarded to Box Number advertisers. Although *The Western Journal of Medicine* believes the classified advertisements in these columns to be from reputable sources, we do not investigate the offers made and assume no liability concerning them. The right is reserved to reject, withdraw, or modify all classified advertising copy in conformity with the decisions of the Advertising Committee.

Please Type or Print Advertising Copy

Classified Advertisements Are Payable in Advance
CLASSIFIED ADVERTISEMENTS, THE WESTERN JOURNAL OF MEDICINE
2 WEST TAUNTON AVENUE, BERLIN, NJ 08009
(609) 768-9360; FAX (609) 753-0064
Ads may be placed online at www.wjmed.com

FAMILY PRACTICE

SOUTHWEST WASHINGTON

Northwest Permanente, P.C., a stable, physician-managed multispecialty group of over 620 physicians providing quality care to 430,000 members of Kaiser Permanente in Oregon and Southwest Washington, has excellent opportunities for board certified or eligible family physicians. Our medical offices in Vancouver, Washington have an outpatient clinical position that includes some urgent care; and our group in Longview has an opening for an FP with or without OB skills.

Our program offers a professionally stimulating practice in one of the most successful managed care systems in the country. We also offer a competitive salary (signing bonus for Longview), and a full benefits package including a generous retirement program, professional liability coverage, sabbatical leave and more. To receive additional information, please forward inquiry and CV to: W.J. Clark, Director of Professional Resources, Northwest Permanente, P.C., 500 NE Multnomah, Suite 100, Portland, OR 97232-2099. (800) 813-3763. EOE.

KAISER PERMANENTE
Northwest Permanente, P.C.
Physicians and Surgeons

IDAHO

Make One Of America's Best Places to Live Even Better.

Where You'll Work.
Primary Health, Idaho's largest, fastest-growing integrated health care system whose network of family medicine immediate care centers, by-appointment family practitioners, pediatricians and OB/GYNs serves beautiful southern Idaho.

Where You'll Live.
In a great place to raise a family with quality schools, incredible outdoor recreation and a rural atmosphere close to a metropolitan area with a beautiful performing arts center, excellent hospitals and professional sports.

What You'll Get.
The financial backing and medical resources of a major health care network. A competitive salary, ownership options, flexible work and call schedules, professional growth, full benefits including medical and dental and much more

Submit CV and questions to:
BECKY NELSON
(800) 688-5008 ext 507 • FAX (208) 344-4262
Physician Recruitment
800 Park Boulevard, Suite 760
Boise, Idaho 83712

Primary Health

CALIFORNIA

Int-rim PHYSICIANS

LOCUM TENENS
PERMANENT PLACEMENTS

Jim Ellis (800) 437-7676

PHYSICIANS WANTED

RENO: General Internists. University of Nevada School of Medicine. Four full-time faculty positions available January 1, 1999 at University-affiliated hospitals and clinics. Duties: adult inpatient and ambulatory patient care; medical resident/student supervision and instruction; administrative duties including day-to-day resident supervision and scheduling, committee participation, conducting morning report and board reviews; teaching ability/experience is highly desirable. Requirements: MD or DO; BC or within two years of graduation from an ACGME-approved Internal Medicine Residency Program (with a strong likelihood of board certification based on academic record); must qualify for Nevada license and malpractice; good working knowledge of VA Medical Center and for-profit hospital systems related to residency training programs. CV and names of 3 references to William Graettinger, MD, Search Committee Chair, University of Nevada School of Medicine, Department of Internal Medicine, 1000 Locust Street (111), Reno, NV 89520, (702) 328-1427, FAX (702) 328-1769. Applications received by December 2, 1998 are assured full review. AA/EOE.

OCCUPATIONAL MEDICINE Locum Tenens Pacific Northwest - Northwest Permanente, P.C., a physician-managed, multispecialty group, has a full-time, six-month to one-year locum tenens opportunity available for a Board Certified and/or residency trained occupational medicine physician or other relevant primary care trained physician, at our medical offices in Oregon and Southwest Washington. Our Occupational Health Program has 19 physicians and covers outpatient clinics at nine sites with 65,000 visits per year, an Employee Health Service, and an Environmental Safety Program serving nearly 6,000 employees. We offer a competitive salary and benefit package which includes family medical insurance, paid time off, professional liability coverage, and a relocation allowance. Please forward C.V. to: W.J. Clark, Director of Professional Resources, NORTHWEST PERMANENTE, P.C., 500 NE Multnomah St., Suite 100, Portland, OR 97232-2099. (800) 813-3763. EOE.

FAMILY PRACTICE - MILWAUKEE, WISCONSIN LAKESIDE: Join two board certified family physicians in a unique practice opportunity-integrated health care for women and their families with a health plan focused on wellness through holistic, preventative programs including yoga, acupuncture, massage, stress management, etc. OB is optional, excellent and flexible call arrangement, teaching opportunities also available. Brand new beautiful clinic with a unique design, comprehensive benefit package. Call Laurie Myers, 800-338-7107 or fax CV 414-427-7251 or e-mail: fha@execpc.com

THE 12TH ANNUAL STATE-OF-THE-ART ECHOCARDIOGRAPHY. February 15-18, 1999. Tucson, Arizona. 25 Category 1 credit hours. Fees before February 1: $590 for ACC members; $685 for non-members; $490 for fellows-in-training, residents, nurses, physician assistants, and technologists. Additional $50 after February 1. For information, call American College of Cardiology, Extramural Programs, 800-253-4636, ext. 695; (outside U.S. and Canada, 301-897-5400, ext. 695); FAX 301-897-9745.

PHYSICIANS WANTED

NINTH ANNUAL ECHO HAWAII 1999. February 1-5, 1999. Kohala Coast, Big Island, Hawaii. 24.5 Category 1 credit hours. Fees before January 18: $590 for ACC members; $695 for non-members; $495 for fellows-in-training, residents, nurses, physician assistants, and technologists. Additional $50 after January 18. For information, call American College of Cardiology, Extramural Programs, 800-253-4636, ext. 695; (outside U.S. and Canada, 301-897-5400, ext. 695); FAX 301-897-9745.

OREGON AND THE NORTHWEST. Urban, suburban, rural locations; variety of practice arrangements; all specialties. Placement professionals for 20 yrs. Oberto & Associates, 920 Pinecrest Terr, Ashland, OR 97520. (800) 482-6656; FAX (541) 482-4951. No J-1 Opp. boberto@jeffnet.org.

WESTERN STATES OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 100 positions of various specialties. Both permanent and locum tenens. Send CV to:

Western States Physician Services
7510 No. Trellis Circle, Fresno, CA 93720
Call (800) 873-0786; FAX (800) 705-7943
email: weserve@lightspeed.net

Since 1979
the

Interim PHYSICIANS.

LOCUM TENENS NETWORK has been taking the hassles of the paperwork and overhead out of practicing medicine. Practice near home or travel the country. We will coordinate all your travel details and provide you with the best occurrence malpractice policy available. Explore a partnership with Interim Physicians and open new horizons for your future.

Call today! (800) 333-7828

The Western Journal of Medicine

www.wjmed.com

Practical Information for Practicing Physicians

California Department of Corrections

As one of the largest, most unique and stable employers of health care professionals, we currently have administrative opportunities in several locations for California licensed:

CHIEF PHYSICIAN & SURGEON (Board Eligible, Board Certified)
Opportunities exist for California Licensed Physicians to provide leadership to our Physician teams at our Hospitals & Correctional Treatment Centers. Supervisory and administrative experience required. Positions available at: Richard Donovan Correctional Facility, San Diego; California State Prison, Corcoran, and Centinela State Prison, Imperial.

CHIEF MEDICAL OFFICER (Board Certified)
Excellent opportunities for Physicians responsible for the high standards of the quality assurance/management of the Medical, Mental Health, Pharmacy, and Dentistry programs in our Correctional Facilities. Opportunities exist at High Desert State Prison, Susanville.

CHIEF PSYCHIATRIST (Board Eligible, Board Certified)
In this lead position, your prior supervisory experience and administrative background are a definite asset. You will direct and manage our collegial team of professionals in one of the following locations: Central California Women's Facility, Chowchilla; California Substance Abuse Treatment Facility and State Prison, Corcoran; North Kern State Prison, Delano; Wasco State Prison, Wasco; and High Desert State Prison, Susanville.

Generous benefit plan with holidays, vacation, professional liability coverage, possible 24-month waiver for CA license pending, safety retirement, medical/dental/vision plans and much more.

Contact Medical Recruiter, Health Care Services Division, P.O. Box 942883, Sacramento, CA 94283-0001. Phone: 916-327-7081. Fax: 916-327-1436. Online: www.sbg.ca.gov. EOE.

HEALTH CARE SERVICES DIVISION
CALIFORNIA DEPARTMENT OF CORRECTIONS
PUBLIC SAFETY. PUBLIC SERVICE

11/98

The Western Journal of Medicine

Reprints

Any article printed in *WJM* can be purchased in quantities of 100 or more. Printed on fine quality journal stock.
Prices are based upon article length and quantity ordered.

Call Walter Finley for prices and information, 8:30 – 5:30 EST, Mon– Fri, (804) 979-8034 ext. 146; or E-Mail to: wjm@cjp.com

ADVERTISING INDEX

SUCCESSFUL AGING ORDER FORM . . . . . .2nd Cover
SOUTHERN MEDICAL ASSOCIATION . . . . . .3rd Cover
THE QUEST FOR MERCY ORDER FORM . . . . . .4th Cover

The Western Journal of Medicine

Practical Information for Practicing Physicians

Subscribe Now!

The Western Journal of Medicine extends its thanks to the loyal CMA members who have already made their commitment by subscribing to *WJM*. Here is your opportunity to support the revitalized *Journal*...**now available through subscription only.**

Your subscription to *WJM* features:

EPITOMES
Highlights of major advances in a different specialty each month with brief epitomes by experts in the field.

BIOMEDICAL SCIENCE
Five clinical research societies coordinate important new research findings, emphasizing clinical value.

SOCIOECONOMICS
WJM is often the first to predict, examine, and evaluate socioeconomic changes and trends.

CONFERENCES
All you need to know about medical conferences, nationally and locally.

EDITORIAL LEADERSHIP
Linda Hawes Clever, MD, will extend *WJM's* reach and impact in medical circles around the world.

The future of *WJM* is brighter than ever. Subscribe now so you won't miss a single monthly issue. Only **$45** per year for affiliated association members (**$65** for regular subscribers).

There are four easy ways to subscribe...

1 ***Call (804) 817-2000*** or

2 ***Fax this ad to (804) 817-2020*** or

3 ***Sign up online at www.wjmed.com*** or

4 ***Mail this ad to the address below***

...and there are three easy ways to pay:

Charge my: ☐ Visa ☐ MasterCard ☐ Check enclosed ☐ Bill me

Name on card _____

Card # _____ Exp. Date _____

Signature _____

Name _____

Address _____

City, State, Zip _____

Phone _____

Fax _____ E-Mail _____

The Western Journal of Medicine

Check One (12 issues):

☐ $45 Member Rate

☐ $65 Regular Rate

☐ $20 Student/Resident/Intern

☐ $90 Institutional Rate

Return to: *The Western Journal of Medicine,* 1224 West Main Street, Suite 200, Charlottesville, VA 22903-2858.
Phone (804) 817-2000. Fax (804) 817-2020.

LAC

1999 EDUCATIONAL CALENDAR

SOUTHERN MEDICAL ASSOCIATION

Your CME Resource!

ruary 19-21	**2nd Annual Conference on Osteoporosis: Diagnosis, Treatment and Prevention in Primary Care** Indian River Plantation Marriott Stuart, Florida
ch 4-6	**Southern Orthopaedic Association's 9th Annual SEC Sports Medicine Symposium** Atlanta Hilton and Towers Atlanta, Georgia
ch 12-14	**4th Conference on Pain Management: Strategies for Improving Outcomes** Sandestin Beach Hilton Destin, Florida
ch 26-28	**New Drugs Update 1999** Hyatt Regency Hilton Head Hilton Head Island, South Carolina
ch 27- April 3	**Southern Orthopaedic Association's Hot Topics in Cold Weather II** Snowmass Resort Snowmass, Colorado
il 9-11	**Management Challenges in Chronic Diseases** Marriott Sawgrass Resort Ponte Vedra, Florida
il 9-11	**Spring Managed Care Update** Westin Hilton Head Hilton Head Island, South Carolina
21-23	**Hot Topics in Primary Care** Marriott Marina Ft. Lauderdale, Florida
e 11-13	**3rd Annual Conference on Hypertension** The Inn at Kiawah Island Resort Kiawah Island, South Carolina
e 13-16	**23rd Annual Sea Island Symposium on Lung Diseases** The Cloister Sea Island, Georgia
e 25-27	**4th Annual Meeting of the Southern Association for Primary Care** Chateau on the Lake Resort Branson, Missouri
July 9-11	**8th Conference on General Surgery and Gastroenterology** The Cloister Sea Island, Georgia
July 12-15	**10th Annual Focus on the Female Patient** Kiawah Island Resort Kiawah Island, South Carolina
July 15-17	**16th Annual Meeting of the Southern Orthopaedic Association** The Ritz-Carlton Amelia Island Amelia Island, Florida
July 16-18	**Pediatric & Adolescent Medicine Update** Kiawah Island Resort Kiawah Island, South Carolina
August 5-7	**12th Annual Meeting of the Southern Association for Oncology** Hamilton Princess Hamilton, Bermuda
August 19-21	**Infectious Diseases Conference: An Update for Primary Care Physicians** The Peaks Resort and Spa Telluride, Colorado
August 27-29	**Focus on the Older Patient** The Ritz-Carlton Amelia Island Amelia Island, Florida
August 28-29	**4th Annual Managed Care Conference** Omni Royal Orleans New Orleans, Louisiana
September 17-19	**2nd Annual Conference on Diabetes: Advances in Management & Prevention** Kingsmill Resort Williamsburg, Virginia
November 10-14	**93rd Annual Scientific Assembly of the Southern Medical Association** Wyndham Anatole Hotel Dallas, Texas
December 3-5	**12th Annual Region IV Burn Seminar** Adam's Mark Winston Plaza Winston-Salem, North Carolina

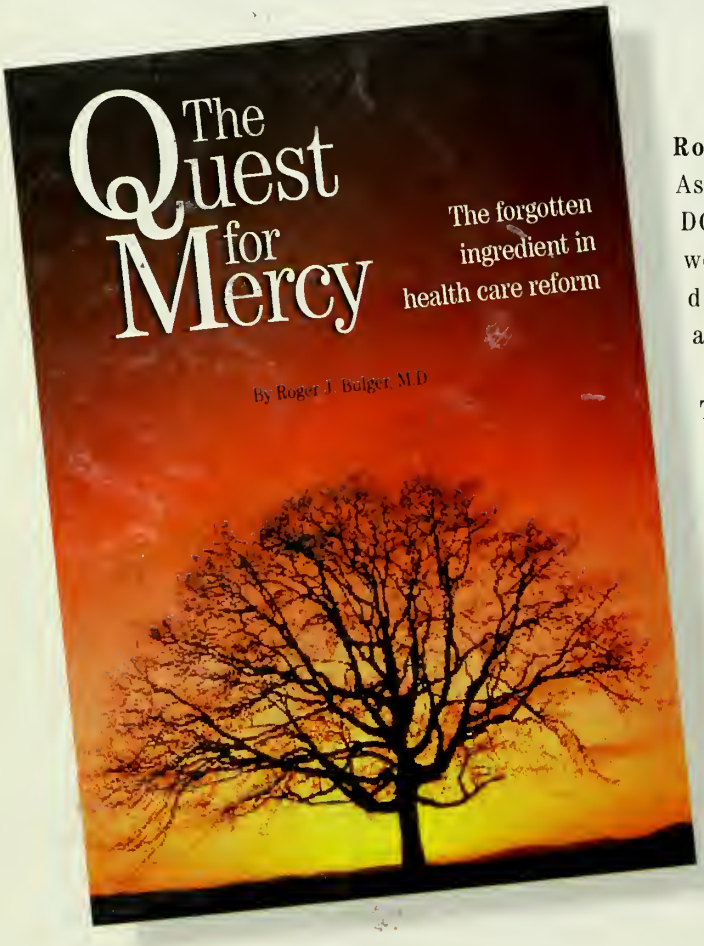
Please call SMA's Education Department at 800-423-4992 for further information on any of these excellent meetings!

***Check us out!* * www.sma.org * On-line CME!**

The Quest for Mercy

The forgotten ingredient in health care reform

by Roger J. Bulger, MD, FACP



Roger J. Bulger, MD, FACP is President of the Association of Academic Health Centers in Washington, DC. He has published scores of papers and chapters, as well as three books on subjects ranging from infectious diseases to medical education, humanities, Hippocrates, and, of course, academic health centers.

The Quest for Mercy is aimed at physicians, including young physicians and medical students. The book addresses managed care and managed cost, sickness and healing, hope and despair, relationships, oaths, populations, prevention, and patients.

"This book will become a classic."

Linda Hawes Clever, MD
Editor, THE WESTERN JOURNAL OF MEDICINE

The Complete Manuscript As Published In
The Western Journal of Medicine

ORDER YOUR COPIES NOW!

Per Copy: $10.00*

*Note: USA/Canada postage and handling included, all other countries please add US $6.00 Air Printed Matter postage. Please add Virginia and local sales tax where applicable. Quantity discounts available; please call.

I would like to order_____copy(ies) of **The Quest For Mercy**.

Payment must accompany order. Total amount enclosed $_____

NAME _____

INSTITUTION _____

ADDRESS _____

CITY/STATE/ZIP _____

COUNTRY _____

❑ Check Enclosed $_____ *please charge my* ❑ VISA ❑ MASTERCARD
(*make payable to:* The Western Journal of Medicine)

Account #_____ Exp. date _____

Signature _____

CARDEN JENNINGS
PUBLISHING CO., LTD.

MAIL TO: *The Western Journal of Medicine*, 1224 West Main Street, Suite 200, Charlottesville, Virginia 22903-2858
Phone: (804) 979-8034 • Fax: (804) 979-4025 • www.wjmed.com

OFFICIAL JOURNAL OF

KA MEDICAL ATION | ARIZONA MEDICAL ASSOCIATION | CALIFORNIA MEDICAL ASSOCIATION | DENVER MEDICAL SOCIETY | IDAHO MEDICAL ASSOCIATION | NEVADA STATE MEDICAL ASSOCIATION | NEW MEXICO MEDICAL SOCIETY | UTAH MEDICAL ASSOCIATION | WASHINGTON STATE MEDICAL ASSOCIATION | WYOMING MEDICAL SOCIETY

DISPLAY SHELVES

The Western Journal of Medicine

VOLUME 169 • NUMBER 6 DECEMBER 1998

ARTICLES

337 Patient Attitudes About Mandatory Reporting of Domestic Violence— Implications for Health Care Professionals
MA RODRIGUEZ, AM CRAIG, DR MOONEY, and HM BAUER

342 Occupational Asthma—Practical Points for Diagnosis and Management
WG KUSCHNER, RK CHITKARA, and PSA SARINAS

351 Controversies in Perioperative Medicine
HQ CHENG

356 A Randomized Double-Blind Study of the Effect of Distant Healing in a Population With Advanced AIDS—Report of a Small Scale Study
F SICHER, E TARG, D MOORE and HS SMITH

364 Prevalence of Antimicrobial Drug–Resistant *Streptococcus pneumoniae* in Washington State
PA FRICK, DJ BLACK, JS DUCHIN, S DELIGANIS, WM MCKEE, and TR FRITSCHE

EPITOMES

370 Important Advances in Preventive Medicine and Public Health

ALERTS, NOTICES, AND CASE REPORTS

380 Mushroom Poisoning due to Amatoxin—Northern California, Winter 1996–1997
EG YAMADA, J MOHLE-BOETANI, KR OLSON, and SB WERNER

385 Thrombophilia in Ischemic Stroke
A POTTI, KM RABADI, and DD WILLARDSEN

386 Acquired Sulfhemoglobinemia—An Underreported Diagnosis?
M NOOR, and E BEUTLER

COMMENTARY

390 Shuffling Off This Mortal Coil—A Shakespearean Perspective on Death and Dying
HW WALLING

OTHER FEATURES

332 Continuing Medical Education Activities

395 Erratum

396 Poem

397 Classified Advertising

399 Subscription Information

Detailed Table of Contents: 330, 331

THE FRANCIS A. COUNTWAY LIBRARY OF MEDICINE BOSTON, MA

DEC 18 1998

Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Medical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology

Full text, free access.

eBMJ

– Fully searchable archive –

– 150 topic collections –

– Customised email alerting –

– Rapid responses –

– Enhanced articles –

– Extra news stories –

– Direct Medline access –

– Jobs, courses, and careers –

And we don't ask you to pay, subscribe, register, provide passwords, or fill in interminable online questionnaires.

www.bmj.com

THE FRANCIS A. COUNTWAY
LIBRARY OF MEDICINE
BOSTON, MA
DEC 18 1998

329

The Western Journal of Medicine®

SINCE 1902

1224 WEST MAIN STREET, SUITE 200 • CHARLOTTESVILLE, VIRGINIA 22903-2858
TELEPHONE (804) 817-2000; FACSIMILE (804) 817-2020; E.MAIL wjm@cjp.com

LINDA HAWES CLEVER, MD, *Editor*
EDWARD D. HARRIS JR, MD, *Associate Editor*

WALTER G. FINLEY, *Managing Editor*
JANET SHAFER, *Production Manager*
DAVID ERN, *Marketing Director*

editorial communications to DR CLEVER • business communications to MR FINLEY

Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Medical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

SPECIAL EDITORS

Special Editor for Arizona
Marshall B. Block, Phoenix, Ariz

Special Editor for Denver
David Shander, Denver, Colo

Special Editor for Idaho
E. R. W. Fox, Coeur d'Alene, Idaho

Special Editor for Nevada
Anton P. Sohn, Reno, Nev

Special Editor for New Mexico
I. Brian Taylor, Carlsbad, NM

Special Editor for Utah
C. Basil Williams, Salt Lake City, Utah

Special Editor for Washington
David Hopkins, Federal Way, Wash

Special Editor for Wyoming
Joseph P. Murphy, Casper, Wyo

ASSISTANT EDITORS

Clinical Investigation
H. Benfer Kaltreider

Health and Public Policy
Ralph Crawshaw

International Health
Anvar Velji

Lessons From the Practice
Stephen J. McPhee
Jonathan E. Rodnick

Medical Staff Conferences
Nathan M. Bass

Poetry
Margaret Kaufman

Primary Care Medicine
Stephen J. McPhee
Terrie Mendelson

Radiologic Cases
Jonathan M. Levy

EDITORIAL BOARD

Editor Emeritus
Malcolm S. M. Watts, San Francisco, Calif

Anesthesiology
Carol Lake, Sacramento, Calif

Biostatistics and Epidemiology
Virginia L. Ernster, San Francisco, Calif

Cardiac and Thoracic Surgery
Norman E. Shumway, Stanford, Calif

Dermatology
Clifton R. White Jr, Portland, Ore

Emergency Medicine
William A. Boehm, Alamogordo, NM

General and Family Practice
Norman Kahn, Kansas City, Mo
Thomas E. Norris, Seattle, Wash
Joe Schoeber, Casper, Wyo

Internal Medicine
Albert Deisseroth, Houston, Texas
Alan Fogleman, Los Angelas, Calif
Patricia Gabow, Denver, Colo
John H. Holbrook, Salt Lake City, Utah
Philip Hopewell, San Francisco, Calif
Irwin J. Schatz, Honolulu, Hawaii
Walter E. Stamm, Seattle, Wash
Reginald Strickland, Albuquerque, NM
Stephen I. Wasserman, San Diego, Calif

Neurology
Robert Collins, Los Angeles, Calif
John Greenlee, Salt Lake City, Utah
Leslie Wiener, Los Angeles, Calif
Earl Zimmerman, Portland, Ore

Neurosurgery
George A. Ojemann, Seattle, Wash
Robert F. Spetzler, Phoenix, Ariz

Nuclear Medicine
Jerold M. Lowenstein, San Francisco, Calif

Obstetrics and Gynecology
Daniel Mishell Jr, Los Angeles, Calif

Occupational Medicine
Linda Rosenstock, Washington, DC

Ophthalmology
Sandy Feldman, La Jolla, Calif

Orthopedics
Thomas DeCoster, Albuquerque, NM

Pathology
Ronald Weinstein, Tuczon, Ariz

Pediatrics
Allen W. Mathies Jr, Pasadena, Calif
Diane Wara, San Francisco, Calif

Pharmacology
Rubin Bressler, Tucson, Ariz

Physical Medicine and Rehabilitation
Julie G. Madorsky, Pomona, Calif

Preventive Medicine and Public Health
Joseph L. Lyon, Salt Lake City, Utah

Psychiatry
J. Christian Gillin, San Diego, Calif
Lewis Judd, La Jolla, Calif

Radiology
Gary Glazer, Stanford, Calif
Michael L. Manco-Johnson, Denver, Colo
Albert A. Moss, Seattle, Wash

Surgery
Haile T. Debas, San Francisco, Calif
Alex G. Little, Las Vegas, Nev

Urology
Linda Shortliffe, Stanford, Calif

Senior Members at Large
Thomas Elmendorf, Davis, Calif
Edgar Wayburn, San Francisco, Calif

ADVISORY BOARD, CLINICAL INVESTIGATION

Brian A. Cason, San Francisco, Calif
John Christenson, Salt Lake City, Utah
Kari Connolly, San Francisco, Calif
Bruce W. Goldberg, Portland, Ore
Philip Goodman, Reno, Nev
Roy Jones, Albuquerque, NM
Howard Lien, Tucson, Ariz
Barbara M. Lippe, Los Angeles, Calif
Michael W. McDermott, San Francisco, Calif
Jeanette Mladenovic, Denver, Colo
Kenneth M. Moser, San Diego, Calif
James C. Orcutt, Seattle, Wash
John Owings, Sacramento, Calif
Robert Robbins, Stanford, Calif
Henry Rosen, Seattle, Wash
Mary H. Samuels, Portland, Ore
George A. Sarosi, San Jose, Calif
Jeffrey Saver, Los Angeles, Calif
David Schriger, Los Angeles, Calif
Jack H. Simon, Denver, Colo
Peggy Sue Weintrub, San Francisco, Calif
Owen M. Wolkowitz, San Francisco, Calif

DISPLAY & CLASSIFIED ADVERTISING INFORMATION

CONTACT: MJ Mrvica Associates, Inc, 2 West Taunton Ave, Berlin, NJ 08009 • (609) 768-9360/FAX (609) 753-0064
Advertisements—The journal is published the second week of the month. Display advertising must be received no later than the first of the month preceding issue. Advertising rates will be sent on request. Acceptance of advertising is contingent upon approval by the Publisher.
The journal reserves the right to reject any advertisement.

SUBSCRIPTION INFORMATION

The subscription price is $70 per year and $130 for 2 years in the United States and Canada (US funds); $85/$160 in all other countries. Institutional rate in the United States is $120/$240; $130/$260 all other countries. Single copies are $10. Special issues are $10. Address all subscription communications to:

THE WESTERN JOURNAL OF MEDICINE Circulation, 1224 W Main St, Suite 200, Charlottesville, VA 22903-2858. • Tel: (804) 817-2000

Allow six weeks for subscriptions to begin. Past issues must be bought individually. So long as reserve stocks are available, missing issue requests from subscribers are honored for up to six months after the issue date. Thereafter, the single copy rate of $10 is applicable for each issue available. Special issues are $10.

Change of Address—Requests for change of address should give both the old and new address. Allow six weeks for changeover.

SUBMITTING MANUSCRIPTS

Manuscripts for consideration should be sent to the managing editor, Walter Finley, 1224 W Main St, Suite 200, Charlottesville, VA 22903-2858.

"Instructions for Authors"—A complete guide to manuscript submission and *WJM* style available from the publisher. Manuscripts may be prepared in accordance with the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals."

PUBLISHER

Copyright © 1998 by the British Medical Journal Publishing Group • Owned and Published by the British Medical Journal Publishing Group

All material subject to this copyright appearing in THE WESTERN JOURNAL OF MEDICINE may be photocopied for the noncommercial purpose of scientific or educational advancement. Volumes begin with January and July.

THE WESTERN JOURNAL OF MEDICINE (ISSN 0093-0415/USPS 084 480) is published monthly by Carden Jennings Publishing Co, Ltd, 1224 W Main St, Charlottesville, VA 22903-2858. Periodicals postage paid at Easton, Pennsylvania.

POSTMASTER: Send address changes to *The Western Journal of Medicine*, Circulation, 1224 W Main St, Suite 200, Charlottesville, VA 22903-2858.

The Western Journal of Medicine

VOLUME 169 • NUMBER 6 • DECEMBER 1998

CONTENTS

ARTICLES

337 **Patient Attitudes About Mandatory Reporting of Domestic Violence—Implications for Health Care Professionals**

MICHAEL A. RODRIGUEZ, MD, MPH; ANDREA M. CRAIG, MSW, MPH; DONNA R. MOONEY, JD; and HEIDI M. BAUER, MD, MPH

From the Department of Family and Community Medicine, Hastings College of the Law, and the School of Medicine, University of California San Francisco; the Pacific Center for Violence Prevention, San Francisco General Hospital; and the San Francisco Injury Center, San Francisco, California.

342 **Occupational Asthma—Practical Points for Diagnosis and Management**

WARE G. KUSCHNER, MD; RAJINDER K. CHITKARA, MD; and PRISCILLA S.A. SARINAS, MD

From the Division of Pulmonary and Critical Care Medicine, Department of Medicine, Stanford University School of Medicine, Veterans Affairs, Palo Alto Health Care System, Palo Alto, California.

351 **Controversies in Perioperative Medicine**

HUGO QUINNY CHENG, MD

From the Division of General Internal Medicine, School of Medicine, University of California, San Francisco, California.

356 **A Randomized Double-Blind Study of the Effect of Distant Healing in a Population With Advanced AIDS—Report of a Small Scale Study**

FRED SICHER, MA; ELISABETH TARG, MD; DAN MOORE II, PhD; and HELENE S. SMITH, PhD

From the Geraldine Brush Cancer Research Institute, California Pacific Medical Center; Sausalito Consciousness Research Laboratory; and Departments of Psychiatry, Statistics, and Medicine, University of California, San Francisco, California.

364 **Prevalence of Antimicrobial Drug–Resistant *Streptococcus pneumoniae* in Washington State**

PAMELA A. FRICK, PharmD; DOUGLAS J. BLACK, PharmD; JEFFREY S. DUCHIN, MD; SAM DELIGANIS, MBA; WILLIAM M. MCKEE, MD; and THOMAS R. FRITSCHE, MD, PhD

From the Schools of Pharmacy and Medicine, University of Washington; Northwest Pharmaceutical Research Network; and PRO-West, Seattle, Washington.

EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

Preventive Medicine and Public Health

Items of progress in preventive medicine and public health. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, as to both scientific fact and important clinical significance.

370 **New Vaccines for Infectious Diseases**

STEVE WATERMAN, MD, MPH, and CURTIS FRITZ, DVM, MPVM, PhD

371 **New Tests for Detecting HIV Infection**

THERESA A. WOEHRLE, MD, MPH, and BERNARD BRANSON, MD, CDC

372 **Hepatitis C**

KAREN L. LINDSAY, MD, and JON ROSENBERG, MD

373 **Indoor Environmental Quality**

JAMES E. CONE, MD, MPH

374 **Update on Public Health in Correctional Facilities**

MICHAEL PUISIS, DO

375 **Acute Effects of Exposure to Methyl Tert-butyl Ether in Gasoline**

ROB McCONNELL, MD, and ROBERT TABER, MD, MPH

375 **Motor Vehicle Occupant Protection for Children**

PHYLLIS AGRAN, MD, MPH; DIANE WINN, RN, MPH; and CRAIG ANDERSON, DHSc, PhD

377 **Asthma—The Shift from Episodic Treatment to Ongoing Prevention, Education, and Management**

EILEEN G. YAMADA, MD, MPH

377 **Influenza**

SANDRA GROSS-SCHULMAN, MD, MPH, RN; DAVID E. DASSEY, MD, MPH; and LAURENE MASCOLA, MD, MPH

ALERTS, NOTICES, AND CASE REPORTS

380 **Mushroom Poisoning due to Amatoxin—Northern California, Winter 1996–1997**

EILEEN G. YAMADA, MD, MPH; JANET MOHLE-BOETANI, MD; KENT R. OLSON, MD; and S.B. WERNER, MD, MPH

From the Preventive Medicine Residency, the Chronic Disease Control Branch, and the Disease Investigations and Surveillance Branch, California Department of Health Services, Sacramento and Berkeley, California; and the California Poison Control System, University of California, San Francisco, California.

385 **Thrombophilia in Ischemic Stroke**

ANIL POTTI, MD; KHALED M. RABADI, MD; and DARIN D. WILLARDSEN, MD

From the Department of Internal Medicine, MeritCare Medical Center, University of North Dakota School of Medicine and Health Sciences, Fargo, North Dakota.

386 **Acquired Sulfhemoglobinemia—An Underreported Diagnosis?**

MUSTAFA NOOR, MD, and ERNEST BEUTLER, MD

From the Division of Graduate Medical Education and General Internal Medicine and the Department of Molecular and Experimental Medicine, Scripps Clinic and the Scripps Research Institute, La Jolla, California.

COMMENTARY

390 **Shuffling Off This Mortal Coil—A Shakespearean Perspective on Death and Dying**

HOBART W. WALLING, MA

From the Department of Pharmacological and Physiological Science, Saint Louis University Health Sciences Center, St. Louis, Missouri.

OTHER FEATURES

332 **Continuing Medical Education Activities**

395 **Erratum**

396 **Poem**

397 **Classified Advertising**

399 **Subscription Information**

★ Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

Continuing Medical Education

ARIZONA • CALIFORNIA, HAWAII, NEVADA • COLORADO • IDAHO • NEW MEXICO • UTAH • WASHINGTON • WYOMING

ARIZONA

The following list of continuing medical education programs in Arizona is compiled by the Arizona Medical Association. All courses listed have been certified as meeting the criteria for Category I of the ArMA CME Certificate and the AMA Physicians Recognition Award. To list Category I continuing medical education programs, please send information to Arizona Medical Association, 810 West Bethany Home Road, Phoenix, AZ 85013; or phone (602) 246-8901.

Brochures and registration forms are available from the contact person or organization sponsoring the program.

CARDIOLOGY

February 7–11, 1999—**International Congress XII on Endovascular Interventions.** Contact: Erika Scott (602) 266-2200 or fax (602) 265-8885. www.endovascularcongress.org

CONTACT INFORMATION

ArMA—Contact: Arizona Medical Association, 810 W Bethany Home Rd, Phoenix, AZ 85013. (602) 246-8901.

Mayo Clinic-Scottsdale—Contact: Postgraduate Courses, Mayo Clinic-Scottsdale, (602) 301-7447.

U of A—Contact: University of Arizona College of Medicine, Arizona Health Sciences Center, Tucson, AZ 85724. (520) 626-7832; (800) 328-5868.

CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Paulette Richardson, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-3387. For more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

November 5–7, 1999—**11th Annual Anesthesiology Update.** Monterey Plaza, Monterey, California. Fri–Sat. Contact (916) 734-5390.

CARDIOLOGY

January 7–10, 1999—**NewEra Cardiac Care: Innovation and Technology.** Marriott's Mountain Shadows Resort, Scottsdale Arizona. Sponsored by the Cardiothoracic Research &Education Forum. Contact: Aligned Management Associates, Inc. P.O. Box 23220, San Diego CA 92193 (760) 751-8841. Fax (760) 751-8842. www.amainc.com

January 18–22, 1999—**The 30th Annual Cardiovascular Conference at Snowmass.** Sponsored by the American College of Cardiology. To be held at Snowmass Conference Center, Snowmass, CO. 23 CME credits. Contact: Registration Secretary, Extramural Programs Dept., American College of Cardiology, 9111 Old Georgetown Rd., Bethesda, MD 20814-1699. Phone (800) 253-4636, ext.695 or Fax (301) 897-9745.

January 29–31, 1999—**Clinical Nuclear Cardiology: Case Review With the Experts. Cardiology Update 1998.** American College of Cardiology at Los Angeles. Thurs.–Sat. Contact: ACC Extramural Programs (800) 253-4636.

February 18–20, 1999—**19th Annual Pathophysiology & Techniques of Cardiopulmonary Bypass.** San Diego Marriott Hotel & Marina. Sponsored by the Cardiothoracic Research &Education Forum. Contact: Aligned Management Associates, Inc. P.O. Box 23220, San Diego CA 92193 (619) 541-1444 or fax (619) 541-1447. www.amainc.com

DERMATOLOGY

January 14–17, 1999—**Practical Dermatology for the Primary Care Physician, San Diego, CA.** Sponsored by Continuing Medical Education Associates. To be held at the Hyatt Regency, La Jolla, San Diego, CA. Method: AV, L, SB, W. Thurs–Sun. 20 hrs credit: AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

March 4–7, 1999—**Practical Dermatology for the Primary Care Physician, Orlando, FL.** Sponsored by Continuing Medical Education Associates. To be held at the Buena Vista Palace at Walt Disney World Village, Orlando, FL. Method: AV, L, SB, W. Thus–Sun. 20 hrs credit: AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

May 23–26, 1999—**Practical Dermatology for the Primary Care Physician, Las Vegas, NV.** Sponsored by Continuing Medical Education Associates. To be held at the Caesars Palace, Las Vegas, NV. Method: AV, L, SB, W. Sun–Wed. 20 hrs credit: AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

EMERGENCY MEDICINE

December 14–18, 1998— **Emergency Symposium II.** UCSD at La Jolla Marriott, San Diego. Mon.–Fri. 32 hrs. Contact: OCME (619) 534-3940.

February 7–12, 1999—**Emergency Medicine: 22nd Annual UCD Winter Conference.** UC Davis at Hyatt Regency Lake Tahoe, Incline Village, NV. Sun–Fri. 24 hrs. $445. Contact: UCD (916) 734-5390.

March 1–2, 1999—**Improving Emergency Department Patient Satisfaction and Reducing Length of Stay.** Las Vegas, Nevada at Harrah's. Contact: CEME, 5330 Primrose Drive, Suite 250, Fair Oaks, CA 95628. (800) 651-2363.

March 1–5, 1999—**Critical Care, Trauma and Emergency Medicine, 37th Annual Symposium.** Sponsored by the University of Southern California School of Medicine, Postgraduate Division. Caesars Palace Hotel, Las Vegas, NV. 27 hrs. Contact Associate Dean, USC Postgraduate Medicine, 1975 Zonal Ave., KAM 307, Los Angeles, CA 90033. (323) 442-2555 or (800) USC-1119 or FAX (323) 442-2152.

April 12–13, 1999—**High Risk Emergency Medicine.** Las Vegas, Nevada at Harrah's. Contact: CEME, 5330 Primrose Drive, Suite 250, Fair Oaks, CA 95628. (800) 651-2363.

May 6–7, 1999—**Challenges in Pediatric Emergency Medicine.** Las Vegas, Nevada at Harrah's. Contact: CEME, 5330 Primrose Drive, Suite 250, Fair Oaks, CA 95628. (800) 651-2363.

May 13–16, 1999—**Outdoor Emergency Medicine, Scottsdale, AZ.** Sponsored by Continuing Medical Education Associates. To be held at the Marriott Camelback Inn, Scottsdale, AZ. Method: AV, L, SB, W. Thurs–Sun. 32 hrs credit: AMA, AOA, AAFP. $750. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

May 20–21, 1999—**High Risk Emergency Medicine.** Las Vegas, Nevada at Harrah's. Contact: CEME, 5330 Primrose Drive, Suite 250, Fair Oaks, CA 95628. (800) 651-2363.

June 3–4, 1999—**Improving Emergency Department Patient Satisfaction and Reducing Length of Stay.** Chicago, IL at the Holiday Inn Chicago City Centre. Contact: CEME, 5330 Primrose Drive, Suite 250, Fair Oaks, CA 95628. (800) 651-2363.

ENDOCRINOLOGY

January 23, 1999—**NewEra in Diabetes Management.** Cypress Foundation at Doubletree Hotel at Fisherman's Wharf, Monterey. Sat. 7 hrs. $105–$125. Contact: The Cypress Foundation (831) 455-1008 or FAX (831) 455-1060.

March 5, 1999—**Diabetes Update: 1999.** UC Davis at Doubletree Hotel, Sacramento, CA. Friday. 7 hrs. $130. Contact: UCD (916) 734-5390.

March 11–13, 1999—**The Fourth International Conference on Continuous Renal Replacement Therapies.** Hotel del Coronado in San Diego, California. Contact: Shirley Kolkey, Complete Conference Management, 1660 Hotel Circle North, #220, San Diego, CA 92108. (619) 299-6673 or fax (619) 299-6675.

ETHICS

March 3, 1999— **Ethical Problems of Daily Practice.** UC Davis at Cancer Center Auditorium, Sacramento. Wed. 6.5 hrs. Contact: UCD (916) 734-5390.

FAMILY PRACTICE/PRIMARY CARE

January 14–17, 1999—**Practical Dermatology for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Regency, SF. Thurs.–Sun. 20 hrs. $575. Contact: Victoria Gonzales, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

January 14–17, 1999—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Regency, SF. Thurs.–Sun. 20 hrs. $575. Contact: Victoria Gonzales, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

February 11–14, 1999—**Office Gynecology and Women's Health for the Primary Care Physician.** Continuing Medical Education Associates at Hyatt Islandia, San Diego. Thurs.–Sun. 20 hrs. $575. Contact: Victoria Gonzales, PO Box 270469, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

February 12–14, 1999—**California Academy of Family Physicians (CAFP) 51 st Annual Scientific Assembly.** San Diego Concourse, San Diego, CA. 40 hrs. Contact: Clark Franklin, CAFP, 114 Sansome Street, Suite 1305, San Francisco, CA 94104-3824. (415) 394-9121 or fax (415) 394-9119.

February 17–19, 1999—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF at Cathedral Hill Hotel, SF. Wed.–Fri. 16 hrs. $400. Contact: UCSF Program Coordinator, Dept. of Family and Community Medicine (415) 476-5250.

February 27–March 2, 1999—**16th Annual OB/GYN Conference.** OCD at Harrahs Tahoe, South Lake Tahoe, NV. Sat.–Tues. 16 hrs. $325. Contact: UCD (916) 734-5390.

March 27, 1999—**Primary Care Gastroenterology.** UC Davis at Cancer Center Auditorium, Sacramento, CA. Saturday. Contact: UCD (916) 734-5390.

April 10, 1999—**Primary Care Orthopedics, Lower Extremities.** UC Davis at Holiday Inn Northeast, Sacramento, CA. Sat. Contact: UCD (916) 734-5390.

April 17, 1999—**Primary Care Cardiology.** UC Davis at Cancer Center Auditorium, Sacramento, CA. Sat. Contact: UCD (916) 734-5390.

April 28, 1999—**Mangement of Benign Uterine Conditions.** UC Davis at Cancer Center Auditorium, Sacramento, CA. Wed. 4 hrs. $50. Contact: UCD (916) 734-5390.

May 14–18, 1999—**Primary Care Essentials, San Francisco, CA.** Sponsored by Continuing Medical Education Associates. To be held at the Grand Hyatt on Union Square, San Francisco, CA. Method: AV, L, SB, W. Thurs–Sun. 32 hrs credit: AMA, AOA, AAFP. $750. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

INFECTIOUS DISEASE

December 10–12, 1998—**Clinical Care of the AIDS Pateient.** UCSF at Palace Hotel, San Francisco. Thurs–Sat. Credit 24 hours. $455. Contact: UCSF (415) 476-5208.

February 5–6, 1999—**Infectious Disease Update: 1999.** UC Davis at Hilton Hotel, Sacramento. Fri–Sat. Contact: UCD (916) 734-5390.

KEY TO ABBREVIATIONS

DREW:	Charles R. Drew Postgraduate Medical School, Office of Continuing Medical Education, (213) 563-4800.
LLU:	Loma Linda University, Continuing Medical Education Programs, (909) 824-4963.
STAN:	Stanford University, Postgraduate Education, (415) 723-5594.
UCD:	University of California, Davis, Office of Continuing Medical Education, (916) 734-5390.
UCI:	University of California, Irvine, Memorial/UCI Center for Health Education, (714) 824-5926.
UCLA:	University of California, Los Angeles, Continuing Education in Medicine and Health Sciences, (310) 794-2620.
UCSD:	University of California, San Diego, Office of Continuing Medical Education, (619) 534-3940.
UCSF:	University of California, San Francisco, Extended Programs in Medical Education, (415) 476-4251.
USC:	University of Southern California, Postgraduate Division, (800) USC-1119.

February 11–13, 1999—**Epidemiology and Prevention of Infectious Diseases: Emerging Infectious Diseases.** UCSF at Crowne Plaza, Union Square, San Francisco. Thurs–Sat. 14.5 hrs. $470. Contact: UCSF (415) 476-5808.

February 21–26, 1999—**Winter Course in Infectious Diseases, Snowmass, Colorado-25th Anniversary Meeting.** Sponsored by the Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine and Research Institute, Palo Alto Medical Foundation. 28 hrs. $75–$350. Contact: Trisha Mitchell, Meeting Coordinator (800) 535-7814 or fax (215) 422-1283.

INTERNAL MEDICINE

March 19–25, 1999—**Internal Medicine, San Diego CA.** Sponsored by Continuing Medical Education Associates. To be held at the Hotel del Coronado, San Diego, CA. Method: AV, L, SB, W. Fri–Thurs. 45 hrs credit: AMA, AOA, AAFP. $895. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

August 22–27, 1999—**New Advances in Internal Medicine.** Embassy Suites, Monterey, CA. Sun–Fri. Contact (916) 734-5390.

NEPHROLOGY

February 4–6, 1999—**Advanced Nephrology: Nephrology for the Consultant.** Sponsored by UC San Diego. To be held at the Coronado Island Marriott Resort, Coronado, CA. 17 hrs credit:AMA. $175, $425. Contact: Shirley Kolkey, 1660 Hotel Circle North, #220, San Diego, CA 92108. Phone (619) 299-6673 or Fax (619) 299-6675; e-mail c-c-m@worldnet.att.net

NEUROLOGY

February 10–12, 1999—**Recent Advances in Neurology.** UCSF at Mark Hopkins Inter-Continental Hotel, San Francisco. Wed–Fri. 15 hrs. $425. Contact: UCSF (415) 476-0318.

OB/GYN

February 11–14, 1999—**Office Gynecology and Women's Health for the Primary Care Physician, San Diego, CA.** Sponsored by Continuing Medical Education Associates. To be held at the Hyatt Islandia, San Diego, CA. Method: AV, L, SB, W. Thurs–Sun. 20 hrs credit: AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

February 25–28, 1999—**Office Gynecology and Women's Health for the Primary Care Physician, Orlando, FL.** Sponsored by Continuing Medical Education Associates. To be held at the Buena Vista Palace at Walt Disney World Village, Orlando, FL. Method: AV, L, SB, W. Thurs–Sun. 20 hrs credit: AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

February 27–March 2, 1999—**16th Annual OB/GYN Conference.** OCD at Harrahs Tahoe, South Lake Tahoe, NV. Sat.–Tues. 16 hrs. $325. Contact: UCD (916) 734-5390.

April 28, 1999—**Mangement of Benign Uterine Conditions.** UC Davis at Cancer Center Auditorium, Sacramento, CA. Wed. 4 hrs. $50. Contact: UCD (916) 734-5390.

September 25–26, 1999—**Ultrasound Update: 1999.** Hilton Hotel, Sacramento, CA. Sat.–Sun. (916) 734-5390.

ORTHOPEDICS

January 14–17, 1999—**Office Orthopedics and Bone Radiology for the Primary Care Physician, San Diego, CA.** Sponsored by Continuing Medical Education Associates. To be held at the Hyatt Regency, La Jolla, San Diego, CA. Method: AV, L, SB, W. Thurs–Sun. 20 hrs credit: AMA, AOA, AAFP. $575. Contact: CMEA Monica L. Lier. (800) 993-2632 or (619) 674-5200.

February 25–28, 1999—**Office Orthopedics and Bone Radiology for the Primary Care Physician, New Orleans, LA.** Sponsored by Continuing Medical Education Associates. To be held at the Royal Sonesta Hotel, New Orleans, LA. Method: AV, L, SB, W. Thurs–Sun. 20 hrs credit: AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

February 25–28, 1999—**Office Orthopedics and Bone Radiology for the Primary Care Physician, Las Vegas, NV.** Sponsored by Continuing Medical Education Associates. To be held at the Caesars Palace, Las Vegas, NV. Method: AV, L, SB, W. Sun–Wed. 20 hrs credit: AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

June 13–18, 1999—**23rd Annual Fingers to the Toes Primary Care Orthopaedics.** To be held at the Stanford Sierra Camp, near South Lake Tahoe, Fallen Leaf Lake, CA. Sun–Fri. Contact (916) 734-5390.

PEDIATRICS

January 29–31,1999—**37TH Clinical Conference Pediatric Anesthesiology.** Disneyland Hotel, 1150 W. Cerritos Avenue, Anaheim, CA 92802. Sponsored by The Pediatric Anesthesiology Foudation. $250-$295. Contact David J Steward, M.B., Program Director, Pediatric Anesthesiology Conference Box #3, Childrens Hospital Los Angeles, P.O. Box 54700, Los Angeles, CA 90054. Phone (213) 669-2262 or Fax (213) 660-8983.

February 14–17, 1999—**Pediatrics Update 1999, San Diego, CA.** Sponsored by Continuing Medical Education Associates. To be held at the Hyatt Islandia, San Diego, CA. Method: AV, L, SB, W. Sun–Wed. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

February 28–March 3, 1999—**Pediatrics Update 1999, Orlando, FL.** Sponsored by Continuing Medical Education Associates. To be held at the Buena Vista Palace at Walt Disney World Village, Orlando, FL. Method: AV, L, SB, W. Sun–Wed. 20 hrs credit:AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

March 19–20, 1999—**Pediatrics Update: 1999.** UC Davis at Cancer Center Auditorium, Sacramento, CA. Fri–Sat. Contact: UCD (916) 734-5390.

May 6–8, 1999—**Advances and Controversies in Clinical Pediatrics.** UCSF at Ritz-Carlton Hotel on Nob Hill, SF. Contact: UCSF (415) 476-5808 or FAX (415) 502-1795.

PLASTIC SURGERY

March 18–20, 1999—**11th Annual Symposium on Aesthetic Surgery.** UCSF at Palace Hotel, San Francisco. Thurs–Sat. 19.5 hrs. $950. Contact UCSF (415) 476-5808.

PRIMARY CARE

February 26–28, 1999—**Management of the HIV-Infected Patient–A Practical Approach for the Primary Care Practitioner.** Le Meridien, New Orleans, LA. Contact: Center for Bio-Medical Communication, Inc. (201) 342-5300 or FAX (201) 342-7555; email cmeinfo@cbcbiomed.com

March 27, 1999—**Primary Care Gastroenterology.** UCDMC, Cancer Center Auditorium, Sacramento, CA. Sat. (916) 734-5390.

April 10, 1999—**Primary Care Orthopedics, Lower Extremities.** Holiday Inn Northeast, Sacramento, CA. Sat. (916) 734-5390.

April 17, 1999—**Primary Care Cardiology.** UCDMC, Cancer Center Auditorium, Sacramento, CA. Sat. (916) 734-5390.

June 5–7, 1999—**8th Annual Primary Care Treatment of Pain.** Tenaya Lodge at Yosemite, Fish Camp, CA. Sat–Mon. (916) 734-5390.

July 25–29, 1999—**19th Annual Current Concepts in Primary Care Cardiology.** Granlibakken Conference Center, Tahoe City, CA. Sun–Thurs. (916) 734-5390.

PSYCHIATRY

January 24–29, 1999—**Annnual Midwinter Program for Psychiatrists.** UC Davis at Hyatt Regency Incline Village, NV. Sun–Fri. 25 hrs. $495.

April 10, 1999—**Psychiatry Update.** UC Davis at Cancer Center Auditorium, Sacramento, CA. Sat. Contact: UCD (916) 734-5390.

RADIOLOGY

February 25–28, 1999—**Up to Date Radiology in the Desert.** Mira Monte Resort, Indian Wells, California. Credit 26 hrs. AMA. $495-$750. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

RESPIRATORY

March 19–20, 1999—**Cystic Fibrosis Caregivers Symposium.** UC Davis at Marriott Hotel, Napa, CA. Fri–Sat. Contact: UCD (916) 734-5390.

SURGERY

January 15–16, 1999—**What's New General Surgery.** UC Davis at Hyatt Regency Sacramento at Capitol Park. Fri–Sat. 13 hrs. $280. Contact: UCD (916) 734-5390.

April 24, 1999—**3rd Annual Organ Transplant Conference.** UCD at Cancer Center Auditorium, Sacramento, CA. Sat. Contact UCD (916) 734-5390.

UROLOGY

December 11–12—**Practical Issues in Human Sexuality and Erectile Dysfunction.** UCSF at Ritz-Carlton Hotel, SF. Fri–Sat. 14.5 hrs. $385. Contact: UCSF (415) 476-5808.

GENERAL/MULTIDISCIPLINARY

January 29–31, 1999—**Research Study Club, 65th Clinical Conference.** To be held at the Universal City Hilton & Towers, CA. 15 hrs credit. $190–$400. Contact: Mrs.Ball (909) 677-4482 or fax (909) 677-7904; email: lbll@aol.com.

April 28–May 8, 1999—**Blue Water Medical Seminar.** Tri City Medical Center at Baja California aboard Royal Star Sportfisher. Wed–Sun. 20 hrs. $3300. Contact: Ronald Mcdak (760) 727-7863.

May 16–19, 1999—**Alternative Medicine, Scottsdale, AZ.** Sponsored by Continuing Medical Education Associates. To be held at the Mariott Camelback Inn, Scottsdale, AZ. Method: AV, L, SB, W. Sun–Wed. 20 hrs credit: AMA, AOA, AAFP. $575. Contact: Victoria Gonzales, P.O. Box 27049, San Diego, CA 92198. (800) 993-2632 or (619) 674-5200.

June 22–29, 1999—**Mindfulness-Based Stress Reduction in Mind-Body Medicine.** To be held at the Mana Lae Retreat Center, Maui, Ha. $995. Contact: Steve Flowers (530) 898-1495.

LOSS PREVENTION

September 22–25, 1999—**Legal Issues in Damaged Brain Injury Cases.** Westin St. Francis Hotel, San Francisco, CA. Wed–Sat. Contact (916) 734-5390.

HOME STUDY/SELF ASSESSMENT

California Physicians' Legal Handbook Series. California Medical Association. Contact: CMA, PO Box 7690, San Francisco 94120-7690. (800) 882-1262.

Breast Cancer, Early Detection and Control. Texas Medical Association. **CD ROM.** $70. 2 hrs. Contact: Texas Medical Association, (800) 880-1300; http://www.texmed.org/health_science/hs_poep.html

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

Tuesday Noon Conferences—**Various Topics in Medicine.** Lutheran Medical Center, Wheat Ridge. Contact: Jean A. Kline, (303) 425-2951.

First Wednesday of Each Month—**Various Topics in Neurology.** Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

Second Wednesday of Each Month—**Cardiovascular Education Series.** St Anthony Hospital at St Anthony Hospital, Denver. Contact: Rose Powell, (303) 629-3678.

February 4–6, 1999—**Neurology For The Non-Neurologist.** Hyatt Regency, Cancun Mexico. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

February 5–7, 1999—**Arrhythmias: Interptretation, Diagnosis & Management** MGM Grand, Las Vegas, NV Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

February 12–14, 1999—**Clinical Endocrinology For Primary Care Physicans.** Beaver Run Resort, Breckenridge, CO.Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

February 19–21, 1999—**Managing Respiratory Diseases.** Marriot's Casa Marina, Key West, FL. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

February 25–27, 1999—**Dermatology For The Non-Dermatologist.** Atlantis Paradise Resort, Bahamas. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

February 26–28, 1999—**Coronary Heart Disease Update.** Hilton Tapatio Cliffs, Scottsdale, AZ. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

March 12–14, 1999—**Dermatology For The Non-Dermatologist.**Riviera Hotel & Casino, Las Vegas, NV. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

March 25–27, 1999—**Neurology For The Non-Neurologist.** Grand Beach Resort, St. Thomas, USVI. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

March 25–27, 1999—**Clinical Endocrinology For Primary Care Physicans.** Marriott's Beach Resort, St. Grand Cayman. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

March 26–28, 1999—**Managing Respiratory Diseases.** Buena Vista Palace,Orlando,FL. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 8–10, 1999—**Coronary Heart Disease Update.** Hyatt Regency, Aruba Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 8–10, 1999—**Clinical Endocrinology For Primary Care Physicans.** The Westin Resort, St John, USVI. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 9–11, 1999—**Arrhythmias: Interptretation, Diagnosis &Management** Hilton Tapatio Cliffs, Scottsdale, AZ. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 9–11, 1999—**Neurology For The Non-Neurologist.** Marriott's Casa Marina, Key West, FL. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 23–25,1999—**Managing Respiratory Diseases.** Bally's, Las Vegas, NV. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 23–25,1999—**Dermatology For The Non-Dermatologist.** Parc Fifty-five, San Francisco, CA. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 30–May 2, 1999—**Dermatology For The Non-Dermatologist.** South Sea Plantation, Captiva Island, FL. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

April 30–May 2, **Clinical Endocrinology For Primary Care Physicans.** Hyatt Regency, New Orleans, LA. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

May 14–16, 1999—**Managing Respiratory Diseases.** Hilton Resort, Hilton Head, SC. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

May 14–16, 1999—**Neurology For The Non-Neurologist.** Bally's, Las Vegas, NV. Fee $375. Contact Linda Main, Meetings Coordinator, Medical Education Resources, 1500 West Canal Court, Suite 500, Littleton, CO 80120-4569. (800) 421-3756, (303) 798-9682 or Fax (303) 798-5731.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado Health Sciences Center, School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver 80262. (303) 372-9050 or (800) 882-9153; FAX (303) 372-9065.

IDAHO

The listing of continuing medical education programs in Idaho is compiled by the Ada County Medical Society. To list CME programs here, please send information at least two months in advance to: Ada County Medical Society, Inc. 305 W. Jefferson, PO Box 2668, Boise, Idaho 83701. (208) 336-2930.

Brochures, course information, and registration forms are available from the contact person or organization.

February 19–21, 1999—**ACMS 40th Annual Medical Winter Clinics.** McCall, Idaho, Shore Lodge Inn. 11.5 hrs. Contact: Judy Barningham (208) 336-2930 or Marie Chester (208) 331-1478.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

Every First and Third Tuesday—**Building and Implementing Clinical Practice Guidelines at the Point of Care.** Contact: Thomas A. Naegele, DO, (505) 275-7267.

SATELLITE COURSES

Contact: Joe Treat or Jim Cato, Immunization Program, (505) 827-2366.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-7477. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

January 6–10, 1999—**MRI at Snowbird**. Cliff Lodge, Snowbird, Utah. Credit 20 hrs. AMA. $400-$650. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773 or fax (770)552-9859; email: webmaster@ryalsmeet.com. www.ryalsmeet.com

MEDICAL GRAND ROUNDS

Weekly—**Grand Rounds in Internal Medicine, Psychiatry, OB/GYN, and Pediatrics.** Contact: UUSM.

Weekly—**Pediatric Grand Rounds.** Contact: PCMC.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 1100, Seattle, WA 98121; or phone (206) 441-9762 or (800) 552-0612.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Ave, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 S Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 340-2058.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Ste 1100, Seattle, WA 98121. (206) 441-9762.

OTHER CME OPPORTUNITIES

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

Annual Meeting and Course: International Spine Imaging Symposium. February 15–17, 1999. Registry Resort, Naples, Florida. Credit 19.5 hrs. AMA. $250–$650. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

Breast Imaging Today and Tomorrow. January 25–28, 1999. Boca Raton Resort and Club, Boca Raton, Florida. Credit 23 hrs. AMA. $495–$695. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

Breast Imaging Today and Tomorrow. February 15–19, 1999. Buena Vista Palace Resort and Spa, Lake Buena Vista, Florida. Credit 23 hrs. AMA. $495–$695. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

Musculoskeletal MR. January 18–22; 1999. The Ritz-Carlton Resort Hotel, West Palm Beach, Florida. Credit 22.5 hrs. AMA. $450–$695. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

Predoctoral Education Conference. February 4–7, 1999. Savannah Marriott Riverfront, Savannah, Georgia. Contact: Ray Rosetta, Meetings and Programs Director, Society of Teachers of Family Medicine, 8880 Ward Parkway, Kansas City, Missouri 64114. Phone (800) 274-2237, ext. 4512.

STFM Family Conference. March 3–7, 1999. Kiawah Resort, Kiawah Island, South Carolina. Contact: Ray Rosetta, Meetings and Programs Director, Society of Teachers of Family Medicine, 8880 Ward Parkway, Kansas City, Missouri 64114. Phone (800) 274-2237, ext. 4512.

5th Annual Neuroradiology: A Comprehensive Review. February 2–6, 1999. The Ritz-Carlton Resort Hotel, West Palm Beach, Florida. Credit 24 hrs. AMA. $450–$695. Contact: Ryals & Associates, Inc., PO Box 1925, Roswell, GA, 30077-1925; (770)641-9773; fax (770)552-9859; email: webmaster@ryalsmeet.com.

32nd Annual Spring Conference. April 28–May 2, 1999. Sheraton Seattle Hotel & Towers, Seattle, Washington. Contact: Ray Rosetta, Meetings and Programs Director, Society of Teachers of Family Medicine, 8880 Ward Parkway, Kansas City, Missouri 64114. Phone (800) 274-2237, ext. 4512.

35th Annual Forensic Dentistry. March 7–11, 1999. Holiday Inn, Silver Spring, Maryland. Credit 38 hrs. $300–$675. Contact: Ruth Murphy, CAME, Armed Forces Institute of Pathology, Washington, DC 20306-6000; (800) 577-3749 or (202) 782-2637; email: came@afip.osd.mil; www.afip.org.

58th Annual American Occupational Health Conference. April 23–30, 1999. Ernest N. Morial Convention Center, New Orleans, Louisiana. Contact: ACOEM Education Dept., 55 W. Seeger Road, Arlington Heights, IL 60005; (847) 228-6850 or fax (847) 228-1856; www.acoem.org.

80th Annual Session-American College of Physicians-American Society of Internal Medicine. April 22–25, 1999. Ernest N. Morial Convention Center, New Orleans. Credit 29 hrs. Contact: ACp-ASIM Customer Service (800) 523-1546, ext. 2600; www.acponline.org.

NOTICE

State Associations should send their CME listings for publication to:

Walter G. Finley, Managing Editor
The Western Journal of Medicine
1224 W Main St, Ste 200
Charlottesville, VA 22903-2858

(804) 817-2000 • Fax (804) 817-2020 • wjm@cjp.com

CONFERENCES IN SAN DIEGO
sponsored by
Children's Hospital & Health Center
San Diego, California

- **Current Concepts in Pediatric Medicine,** February 26 - 28, 1999 • 16 CME credits
- **Pediatric Dermatology for the Practitioner,** April 30 - May 1, 1999 • 12 CME credits
- **Current Concepts in Pediatric Allergy and Otolaryngology - Otoscope, Stethoscope and Beyond: Traditional and Alternative Approach to Optimal Outcomes,** July 16 - 18, 1999 • 16 CME credits

For more information contact:
Continuing Medical Education
☎ (888) 892-9249
Fax (619) 495-8587

Articles

Patient Attitudes About Mandatory Reporting of Domestic Violence
Implications for Health Care Professionals

MICHAEL A. RODRIGUEZ, MD, MPH; ANDREA M. CRAIG, MSW, MPH; DONNA R. MOONEY, JD; *and* HEIDI M. BAUER, MD, MPH; *San Francisco, California*

As of January 1994, California physicians are required to report to police all patients who are suspected to be victims of domestic violence. This article describes the results from a focus group study of abused women (n = 51) that explored their experiences with and perspectives on medical care. The eight focus groups included two Latina (total n = 14), two Asian (total n = 14), two African-American (total n = 9), and two Caucasian (total n = 14) groups of women who had been the victims of domestic abuse within the previous 2 years. The women were recruited through community-based organizations in the San Francisco Bay Area. With regard to physician reporting of domestic violence to police, five themes were identified: fear of retaliation by the abuser, fear of family separation, mistrust of the legal system, desire for police protection, and preference for confidentiality and autonomy in the patient–health professional relationship. Our results indicate that mandatory reporting may pose a threat to the safety and well-being of abused women and may create barriers to their seeking help and communicating with health care professionals about domestic violence.

(Rodriguez MA, Craig AM, Mooney DR, Bauer HM. Patient attitudes about mandatory reporting of domestic violence—implications for health care professionals. West J Med 1998 169:337–341)

Domestic violence is a leading cause of morbidity and mortality in women. It is estimated that 4.4 million women in the United States are physically abused by intimate partners each year.[1] Domestic violence victims make up an alarmingly high proportion of women seeking care for trauma and medical and psychological problems.[2–9] Yet, despite the high prevalence of domestic violence victims in healthcare settings, only a small proportion of abused women are identified as such by health care professionals.[10] Because of the high utilization of medical services by victims of domestic violence, health care workers are in a unique position to identify and assist victims of abuse.

Researchers have identified several barriers that affect the ability of both physicians and patients to address the topic of domestic violence. Obstacles to physician inquiry include time constraints, a lack of training or protocols for dealing with domestic violence, discomfort with the topic of abuse, fear of offending patients, and feelings of powerlessness.[2,11] Abused women's reluctance to disclose abuse to their physicians is based on fear of retaliation by the abuser, shame, embarrassment, low self-esteem, and family loyalty.[12]

As the medical community works to improve detection and intervention by health care professionals, lawmakers have responded with a range of legislation. While most states require health care workers to report to the police patients with injuries resulting from illegal acts, a few states have added specific language to include adult victims of domestic violence.[13] In California, health care and other professionals are required to report to the police patients whom they reasonably suspect are suffering from a domestic violence–related injury.[14] The health care professional must notify the police by telephone and submit written findings within 2 days. These reports must include, but are not limited to, the name of the victim, the victim's whereabouts, the extent of the victim's injuries, and the identity of the alleged perpetrator.

California's mandatory reporting law has possible advantages, but it also presents potential disadvantages. Potential benefits include improved crime detection and

From the Department of Family and Community Medicine (Dr Rodriguez), Hastings College of the Law (Dr Mooney), and the School of Medicine (Dr Bauer), University of California San Francisco; the Pacific Center for Violence Prevention (Dr Rodriguez), San Francisco General Hospital; and the San Francisco Injury Center (Dr Craig), San Francisco, California.

Reprint requests to Michael Rodriguez, MD, MPH, Pacific Center for Violence Prevention, San Francisco General Hospital, San Francisco, CA 94110.

Funding for this project was provided by the Robert Wood Johnson Clinical Scholars Program, Stanford University.

data collection, enhanced victim safety through better police protection, increased responsiveness of the health care system, and relief for victims from the onus of reporting.[13] Potential disadvantages include retaliation by abusers, decreased utilization of health care services, and loss of abused women's control over the decision to involve the legal system.[15] Additionally, the patient-physician relationship may be strained when confidentiality is compromised.

Our previous work has addressed barriers to health care for abused female patients,[12] special needs of abused women in patient–health professional interactions,[16] and a legal analysis of mandatory reporting legislation.[15] This article describes abused women's experiences with police and concerns about the consequences of physician reporting to police. These research findings serve as an initial exploration of the impact of mandatory reporting practices.

Methods

Because of the general lack of information regarding patient perspectives on mandatory reporting practices, qualitative research using focus groups was conducted to best elicit the experiences, beliefs, feelings, and attitudes of abused women patients.[17] Semistructured focus group discussions using open-ended questions were designed to elicit participants' experiences with and perspectives about the health care system. In particular, the participants were asked to discuss definitions of domestic abuse; sources of help for problems related to domestic abuse; and the attitudes, feelings, and behaviors that may predispose abused women to seek or avoid seeking help from health care professionals. The original focus group instrument was written in Spanish, translated into English, then translated back into Spanish to verify the accuracy of the translation process. Only minor grammatical differences were noted. The English version was translated into Mandarin and Cantonese; no further back-translation was performed. This study was approved by the Human Subjects Review Committee at Stanford University, and informed consent was obtained from all participants.

Women from four ethnic groups were recruited through community-based organizations that included women's advocacy groups and abused women's resource centers and shelters in the San Francisco Bay Area. Women ages 18 to 64 years who had been victims of domestic abuse within the previous 2 years were eligible to participate. Each of the eight 90-minute focus groups was composed of women with the same ethnic identity and was facilitated by two moderators, at least one of whom was female and matched the ethnic makeup of the group. Two focus groups of Latinas were conducted in Spanish, one focus group of Asian women was conducted in both Mandarin and Cantonese, and all other groups were conducted in English. Discussions were audiotaped, transcribed, and translated into English. The transcripts were not translated back into the original languages.

Based on iterative readings of the transcripts by independent readers, a list of codes was developed to encapsulate topics discussed in the focus groups. Each transcript was subsequently coded by people matched for ethnicity of the focus group participants and by people outside the culture. Coded data were organized using Ethnograph 4.0, software designed for qualitative data analysis. For this article, readers focused primarily on the participants' experiences with the legal system, concerns about police involvement, and perspectives on the legal system's impact on patient–health professional communication. Described here are themes that were discussed in at least three focus groups and among at least three ethnicities.

Results

The study population (n = 51) included 14 Latina women from Mexico, El Salvador, Guatemala, and Colombia who had lived in the United States for 1–15 years; 14 Asian women from China, Vietnam, Korea, the Philippines, and Taiwan who had lived in the United States for 1–22 years; and 9 African-American and 14 Caucasian women born in the United States. Of those women who agreed to participate, attendance rates were 88% (14 of 16) for Caucasian and Latina women, 78% (14 of 18) for Asian women, and 69% (9 of 13) for African-American women. The participants were ages 22 to 60 years with a median age of 34 years. Their formal education ranged from none to university level with a median of 12 years. Forty (78%) of the participants had children.

Participants in all eight focus groups discussed their perspectives on police involvement in domestic violence and physician reporting to police. Specific themes included fear of retaliation by the abuser, fear of family separation, mistrust of the legal system, desire for police protection, and preference for confidentiality and autonomy in the patient–health professional relationship. Although these themes are presented individually, they were highly interrelated. Many participants feared that involving the criminal justice system might lead to further abuse, separation of their families, or other negative consequences. In spite of frustrations with police responses, however, some participants wanted police protection during episodes of violence. Many participants preferred that physicians keep their confidentiality and allow patients to make decisions about when to involve the police.

Fear of retaliation by the abuser

Many of the participants were afraid violence would escalate if a physician report resulted in police intervention. This concern was addressed by all four ethnic groups and arose in seven of the eight focus groups. In some cases, the abused women were reluctant to seek medical care because they believed that police intervention resulting from physician reporting would have dangerous consequences for them. In other cases, the participants lied to health care professionals about the source of their injuries or withheld information about the

abuse to avoid police involvement. Some of the abused women felt that their safety could not be ensured by the police and therefore avoided disclosing their abuse to physicians as a way of preventing future violence.

> I say no way. I'm sorry, but if my doctor were to call the police and they went to my husband, my husband would have beat the shit out of me. I'm sorry, but there has got to be, maybe reported to Battered Women [a local resource center for abused women]. I don't know, but I don't think a doctor should go over your head, go to the police, it's dangerous.
>
> —Caucasian woman

> You don't know. You don't tell the doctor. You're scared of the husband.
>
> —Asian woman

> Oh, okay, but what made it difficult for me to confide [in a physician] was the fact that I feared for my life, you know. And I knew that if I was to tell them what actually happened that they would call the police and I would have to file a report and they couldn't guarantee me that they would be there 24 hours to protect me from this maniac. So, therefore, I wasn't taking that chance on my life....
>
> —African-American woman

Fears of family separation

Some participants were opposed to police involvement because they feared that it might result in separation of their families. This concern was addressed by three ethnic groups and arose in four of the eight focus groups. For some women, dissolution of the family meant loss of the father as the head of household, potential loss of child custody, or loss of the family's financial resources. Some participants believed that a marital separation would be especially harmful to their children. These participants avoided police involvement for the sake of their children and families.

> [My friend] confessed she's been in a battered situation for eight years.... I don't know if she's gone to the hospital or not, but it could ruin it for her. You don't know what will happen to your children. If you're in a battered situation, they'll take your kids, you know.
>
> —Caucasian woman

> But when he beat me too much I went to the hospital ... they told me that next time it happened I should call the police, but I didn't want to cause trouble for my children so I tolerated it. When he beat me, I tolerated it for the sake of my children....
>
> —Asian woman

> I grabbed my children and I went to the police to, how do you say, write the minutes ... but I have not dared to do it ... I fear to hurt the children, I always think of them, even though they do not want to see the violence....
>
> —Latina woman

Mistrust of the legal system

Many of the participants were resistant to police involvement because of previous negative experiences with police and mistrust of the legal system. This concern was addressed by all four ethnic groups and arose in six of the eight focus groups. Negative views of the criminal justice system stemmed from the participants' perception of police officers' negative attitudes toward them, delayed response to calls, insensitivity, and inadequate protection. In addition, some abused women were concerned about possible harm that would come to their partners. Other participants believed that the process of filing a police report and negotiating the court system would be onerous.

> [The police] get tired of coming or they take their time about coming if they know what's wrong.... I mean, so what if you don't follow through the first couple of times. You're going to get enough and follow through one time or another. And they just [say], "All you're going to do is let him come right [back]."
>
> —African-American woman

> What makes it difficult is that ... when you tell the doctor, the doctor is going to call the police and when the police get here, you already been through so much trauma and stuff that ... it's like you just going through it all over again. It's really hard to do because ... you have to go through the whole system ... and at that time, you're not looking to go through all that stuff.
>
> —African American woman

Some participants were afraid that if the police got involved, the victim would be held responsible and arrested for her involvement in the violence. Some participants reported that as a means of discouraging them from contacting the police, their abusive partners would threaten that the victim herself would be arrested. One participant reported that she was arrested for fighting back.

> And I was scared if I called the police, they would take me to jail.... [The perpetrator] said, "You can't call the police 'cause you'll go to jail too."
>
> —African-American woman

> I've had bad experiences with police officers. I've had two times where they've come over; I had to go pick up some things from my house.... Once I got there, [my ex-partner] started physically abusing me. And then he laughed and said, "I'm going to call the police on you because you're in my house."... He did this [assault] to me and the police officers yelled at me. They were rude.... They saw my shirt was ripped, they saw the handprints on me, everything. They did a police report against me.... I'm 120 [pounds] and here's this big guy saying, "She came over and she abused me."
>
> —Caucasian woman

Desires for police protection

Some participants believed that law enforcement plays an important role in protecting victims during violent episodes. This issue was addressed by three ethnic groups and arose in three of the eight focus groups. In fact, two women specifically stated that physician reporting to police relieves patients of the burden and responsibility of making a report.

> Usually my first thought is to call the police [about a battering incident].
>
> —Asian woman

> Until he would bring me thrown on the floor ... in this moment is when one looks at things truly and when one grabs the initiative of calling the police.
>
> —Latina woman

> I think that a doctor can help a lot of women who ask for help in terms of getting cured physically but also that the doctor should pay attention to her emotional ailment ... the doctors should see the need, that if one needs the police in this very place, the doctor can take care of it.... I feel the need that a doctor should take this responsibility of informing the police [about domestic violence]....
>
> —Latina woman

Preference for confidentiality and autonomy

Several of the abused women were concerned that physician reporting to police would infringe on patient-physician confidentiality and autonomy. These concerns were addressed by three ethnic groups and arose in six of the eight focus groups. Some participants remarked that without confidentiality between themselves and their physicians, it would be difficult for them to discuss domestic violence. Furthermore, they believed that they should retain control over decisions about when to involve the police. These participants expressed concern that mandatory reporting would impair the patient–health care professional relationship and diminish their trust in their physicians and in the medical system.

> I was going to say I don't think it would be a good idea, actually, to ask the police and the doctors to cooperate. Because it's hard enough to get the doctor to understand and if you think that it might be going further, you're going to be even more reluctant to say anything.... I think it would make people less apt to tell the doctor what they need to tell him for their own health. They're thinking of all the repercussions.
>
> —Caucasian woman

> What would make it easier for me would be to, um, preferred to be my choice. Well, I need help, can you call the police? Or if, um, this happened to me but I don't want the police involved, can you please treat me and keep my confidentiality? There's supposed to be a law that they keep confidentiality between the patient and the physician.
>
> —African-American woman

A few participants reported that when physicians took action on patients' behalf by documenting the abuse without making a police report, they felt empowered to prosecute the perpetrators when they were prepared to do so. When discussing possible health care interventions, some participants preferred approaches that would permit their physicians to assist them while allowing abused women to control the timing of criminal justice involvement.

> But [the hospital staff told] me that it would ... be up to me to make a full [domestic violence] report. That they would just notify the police that it had happened, but the police would not come out or do anything 'til I had made the report. So the control was still in my hands even though it was good that they did what they did. I felt that was appropriate.
>
> —Caucasian woman

> I think the doctor can ask you whether or not have you been involved in domestic violence and ask you, "Do you want to go through the procedures of pressing charges?" or whatever. And if you say yes, they'll help you out, and if you say no, they'll just put it on your chart and leave it alone....
>
> —African-American woman

Discussion

The results of this study indicate that California's mandatory reporting law may have a number of unintended negative consequences for domestic violence victims. In particular, many of the abused women in our study felt that physician reporting to police potentially jeopardizes the safety of patients, deters abused women from seeking medical services, and compromises medical professional standards of confidentiality and patient autonomy. Their reluctance to involve police was based on their fear of increased violence, concerns about family separation, and mistrust of the police.

Given the many concerns that the participants expressed about the potential consequences of police involvement, it is possible that mandatory reporting practices may create barriers to medical care for abused women. For many abused women, the consequences of reporting may serve as deterrents to seeking help from medical institutions. Interventions that potentially deter victims from seeking health care are undoubtedly problematic. Further research is necessary to assess the impact of mandatory reporting on the utilization of medical services among victims of domestic violence.

Several study participants expressed concerns about the impact of mandatory reporting on confidentiality and patient autonomy. The abused women indicated a desire to maintain confidentiality with their doctors and their ability to make their own decisions. Many participants wanted to discuss domestic violence with their physicians to obtain support and advice. However, they were reluctant to ask their doctors for help given the possibility that their conversations may not be kept confidential or, more importantly, might result in police involvement. Some of the participants chose to avoid talking with physicians about domestic violence to maintain their autonomy. The negative impact of mandatory reporting on confidentiality and autonomy may undermine current efforts by health care professionals to improve the identification and treatment of domestic violence.

This research had several limitations. The sample was small and was not randomly selected. As a result of the method of recruitment, women in our study were likely to have greater community involvement compared with other abused women. Further research should be conducted to determine whether the sentiments of participants presented here are shared by abused women throughout California and in other states.

Policy choices that seek to address the needs of abused women in healthcare settings are necessarily complex. Abused patients and their physicians face significant dilemmas under the current mandatory reporting law. Abused patients may not be sure whether their families are better served by involving the police, which might lead to protection from the abuser or could result in further violence or an unwanted separation of family members. If an abused patient does not want to involve the police, she may choose not to communicate with her physician about the abuse; this may preclude her from receiving much-needed assistance from her doctor, such as treatment of injuries, documentation of the abuse, emotional support, and referrals to domestic violence services. Clearly, research on the impact of mandatory reporting legislation on victims of domestic violence should be conducted before mandatory reporting legislation is enacted elsewhere.

Acknowledgments

We are indebted to the staff of the following agencies in California: the Family Violence Prevention Fund, San Francisco; Mujeres Unidas y Activas, San Francisco; Battered Women's Alternatives, Concord; the Support Network, Mountain View; Asian Women's Shelter, San Francisco; Cameron House, San Francisco; and la Casa de Las Madres, San Francisco, without whose help this study could not have been possible. We wish to thank Marlene Marin, Clara Luz Navarro, Maria Olea, Karen Rosen, MSW, Seline Quiroga, and Ariella Hyman, JD, for their assistance and feedback throughout the project.

REFERENCES

1. Plichta SB. Violence and abuse: implications for women's health. In Falik MM, Collins KS (Eds): Women's Health: The Commonwealthy Fund Survey. Baltimore, MD, Johns Hopkins University Press, 1996, pp 237–270

2. McLeer SV, Anwar R. A study of battered women presenting in an emergency department. Am J Public Health 1989; 79:65–66

3. Conway T, Hu T, Kim P, Bullon A. Prevalence of violence victimization among patients seen in an urban public hospital walk-in clinic. J Gen Intern Med 1994; 9:430–435

4. Gin NE, Rucker L, Frayne S, Cygan R, Hubble FA. Prevalence of domestic violence among patients in three ambulatory care internal medicine clinics. J Gen Intern Med 1991; 6:317–322

5. McCauley J, Kern D, Kolodner K, et al. The "battering syndrome": prevalence and clinical characteristics of domestic violence in primary care internal medicine practices. Ann Intern Med 1995; 123:737–746

6. Freund K, Bak S, Blackhall L. Identifying domestic violence in primary care practice. J Gen Intern Med 1996; 11:44–46

7. Gazmarian JA, Lazorick S, Spitz A, Ballard T, Saltzman L, Marks LS. Prevalence of violence against pregnant women. JAMA 1996; 275:1915–1920

8. MacFarlane J, Parker B, Soeken K, Bullock L. Assessing for abuse during pregnancy: severity and frequency of injuries and associated entry into prenatal care. JAMA 1992; 267:3176–3178

9. Stark E, Flitcraft A. Killing the beast within: woman battering and female suicidality. Int J Health Sci 1995; 25:43–64

10. Hamberger LK, Saunders DG, Hovey M. Prevalence of domestic violence in community practice and rate of physician inquiry. Fam Med 1992; 24:283–287

11. Sugg NK, Inui TI. Primary care physicians' response to domestic violence: opening Pandora's Box. JAMA 1992; 267:3157–3160

12. Rodriguez MA, Quiroga SS, Bauer HM. Breaking the silence: battered women's perspectives on medical care. Arch Fam Med 1996; 5:153–158

13. Hyman A, Schillinger D, Lo B. Laws mandating reporting of domestic violence: do they promote patient well-being? JAMA 1995; 273:1781–1787

14. California Penal Code, section 11160 et seq (West 1992 and Suppl 1995)

15. Mooney D, Rodriguez M. California healthcare workers and mandatory reporting of domestic violence. Hastings Women's Law J 1996; 7:85–111

16. Bauer HM, Rodriguez MA. Letting compassion open the door: battered women's disclosure to medical providers. Cambridge Q Healthcare Ethics 1995; 4:459–465

17. Stillman FA. Focus group research: an overview. In Becker DM, Hill DR, Jackson JS, Levine DM, Stillman RA, Weiss SM (Eds): Health Behavior Research in Minority Populations: Access, Design, and Implementation. Bethesda, MD, US Department of Health and Human Services, 1992, pp 168–175

Articles

Occupational Asthma
Practical Points for Diagnosis and Management

WARE G. KUSCHNER, MD; RAJINDER K. CHITKARA, MD; *and* PRISCILLA S.A. SARINAS, MD; *Palo Alto, California*

Asthma is a common chronic illness characterized by episodes of reversible airflow obstruction. A cornerstone of asthma management is identifying and avoiding agents that cause bronchospasm. The workplace is an important potential source of respirable exposures that can cause or trigger asthma. Identification of an occupational factor in asthma is important: early diagnosis and removal of the worker from the exposure is associated with improved prognosis; the diagnosis of occupational asthma may lead to compensation for work-related impairment and disability; and the diagnosis of occupational asthma is a Sentinel Health Event with implications for public health and prevention. In this article, we review specific causes of occupational asthma and general settings in which an occupational factor should be suspected and explored as part of the management of the worker with asthma. We also review specific and simple elements of history and pulmonary function testing that can be easily assessed by most health care practitioners and may be sufficient to establish a diagnosis of occupational asthma. Finally, we review the medical-legal implications of occupational asthma.

(Kuschner WG, Chitkara RK, Sarinas PSA. Occupational asthma—practical points for diagnosis and management. West J Med 1998; 169:342–350)

Asthma is a common chronic inflammatory disease affecting the airways. It is characterized by episodic airflow obstruction that typically reverses either spontaneously or with treatment. Signs and symptoms include wheezing, cough, chest tightness, and shortness of breath. Asthma is both prevalent and costly. An estimated 15 million people are affected in the United States, including approximately 10 million adults.[1] The total costs of asthma in the United States alone are in excess of $6 billion, including $2.6 billion due to lost work.[2]

The proportion of adult cases of asthma with occupational factors has been estimated at between 5% and 20%.[3,4] Of those diagnosed with occupational asthma, 20% to almost 50% may suffer a reduction in income after the diagnosis is made.[5,6] Work disability resulting in job change was observed in 20% of adults with asthma in one study over a 5-year period.[7] Despite its important adverse impact on health and work, occupational asthma is likely underdiagnosed; even when the diagnosis is suspected, problem management and follow-up is inadequate in as many as half of cases.[8]

Occupational asthma can be defined broadly or narrowly. Broadly defined, occupational asthma is reversible airflow obstruction that is either caused by or exacerbated by a workplace exposure. This very inclusive definition includes cases in which a diagnosis of asthma may antedate a workplace exposure suspected of provoking bronchospasm. In such cases, an occupational exposure may be identified as an important *trigger* of asthma, but it would not be the *cause* of the disease per se. For example, a susceptible food handler who develops bronchospasm when exposed to the refrigerated air of an industrial cold room would, under this definition, have occupational asthma despite the fact that cold air may, of course, be encountered outside of the workplace and despite the fact that cold air exposure is not a cause of asthma per se.

More narrowly defined, occupational asthma includes only those cases of asthma that result from an exposure encountered exclusively at work. In this descriptive model of occupational asthma, a workplace exposure is etiologic; that is, it is the principal *cause* of asthma in the affected worker. In other words, if not for the occupational exposure, the individual would not have asthma. To satisfy this strict case definition, asthma must be newly diagnosed and temporally linked with a workplace exposure that has, either historically or experimentally, been demonstrated to cause asthma in previously healthy workers. An example of this would be new-onset asthma in a health care worker who has had daily exposure to glutaraldehyde since being hired several months previously as an endoscopy technician.[9] In contrast, persons with preexisting asthma who report

From the Division of Pulmonary and Critical Care Medicine, Department of Medicine, Stanford University School of Medicine, Veterans Affairs, Palo Alto Health Care System, Palo Alto, California.

Reprint requests to Dr. Kuschner, 3801 Miranda Ave, Mail Stop 111 P, Palo Alto, CA 94304. E-mail: kuschner@leland.stanford.edu

ABBREVIATIONS USED IN TEXT

RADS = reactive airways dysfunction syndrome
MSDS = Material Safety Data Sheet
FEV_1 = forced expiratory volume in 1 second
TDI = toluene diisocyante
Ig = immunoglobulin
NIOSH = National Institute for Occupational Safety and Health
SENSOR = Sentinel Event Notification System for Occupational Risks

episodes of bronchospasm attributable to nonspecific workplace irritants such as nuisance dust would not fulfill this case-definition of occupational asthma.

While strict operational case definitions of occupational asthma are crucial in epidemiological investigations, they are less relevant in clinical practice. In terms of disease management and particularly with respect to prevention strategies, the more inclusive description of occupational asthma should be adopted. An alternative term for broadly defined occupational asthma is "work-related asthma." Again, this term would include both work-related aggravation of preexisting asthma as well as new-onset asthma caused by a workplace exposure.

An inclusive definition of occupational asthma has been used and advocated by several investigators. Newman-Taylor[10] and subsequently Cartier[11] defined occupational asthma as "variable airways narrowing causally related to exposure in the working environment to airborne dusts, gases, vapours, or fumes." More recently, Wagner and Wegman advocated that occupational asthma be defined as "all asthma caused or exacerbated by workplace exposures—including asthma from sensitizers, irritant-induced asthma, and workplace exposure–induced asthma attacks."[12] In a recent descriptive study of occupational asthma, Wheeler et al defined occupational asthma as a condition meeting the following criteria:

> a patient has asthma and an association between symptoms and the workplace, either documented with specific testing or by clinical history; there has been a workplace exposure, with an association between asthma symptoms and exposure to some process, substance, or environment at work; there are work-related changes in spirometry or peak flow results; or there is a positive response to bronchial provocation testing with the agent to which the patient was exposed at work.[13]

Work-aggravated asthma may be compensable under workers' compensation law. In one recent investigation, Tarlo et al reviewed 609 claims of occupational asthma to a workers' compensation board,[14] of which 469 were found to be associated with workplace exposures. Of those, 50% (or a total of 39% of all claims filed) were cases of asthma aggravated by irritant workplace exposures, while 50% were cases of asthma determined to be caused by the workplace, typically by a known sensitizer such as isocyantes. Importantly, compensation was available for both work-aggravated asthma and asthma thought to be caused by a known sensitizer from the workplace.[14] Additionally, Harber[15] has described a variety of occupation–asthma interactions that should be used to characterize the effect of the workplace on asthma and are relevant to disability reports filed for occupational asthma claimants; included among these is work aggravation of preexisting asthma.

Although clinicians should generally adopt an inclusive view of occupational asthma, it is nonetheless useful to make distinctions between the various types of workplace exposures that may contribute to asthma to develop a more complete understanding of clinical presentation and illness natural history. In considering all those with asthma, a remarkably heterogeneous constellation of factors play roles in disease expression, ranging from emotional to genetic. The spectrum of factors that commonly receive consideration in the evaluation of occupational asthma, however, is more circumscribed and generally limited to inhaled airway stimuli. Still, this represents a very large group; more than 200 occupational agents have been causally linked with asthma.[16] For the purposes of this review, we distinguish between exposures that have been demonstrated to cause asthma, including immune sensitizers, and exposures that aggravate or trigger preexisting asthma.

Occupational Causes of Asthma

The major classifications of occupational exposures that cause new-onset asthma are *1*) high-molecular-weight compounds; *2*) low-molecular-weight compounds; and *3*) high-level-irritant inhalant exposures. Importantly, those who develop asthma after exposure to these inhalants acquire a chronic disease that they presumably would never have developed had they not been exposed. Among susceptible individuals, continued exposure to these inhalants can be expected to result in progressive worsening of asthma.[17]

High-molecular-weight organic compounds include plant and animal proteins, vegetable gums, and wood dusts or barks. Many of these substances induce specific immunoglobulin E (IgE) antibodies, biomarkers of sensitization, in the susceptible worker. Table 1 lists examples of occupations that expose workers to high-molecular-weight compounds that have been causally linked with asthma. A more comprehensive listing may be found elsewhere.[18] Among some exposed workers, asthma symptoms may persist even years after removal from these exposures.[19]

Low-molecular-weight, mostly inorganic, compounds that cause occupational asthma include a variety of chemicals, include isocyanates, which are used to make polyurethane plastics, and metals, drugs, and other chemicals.

One of the most extensively investigated low-molecular-weight substances demonstrated to induce asthma is plicatic acid (440 Da), the primary compound in the Western red cedar and the principal etiologic factor in cedar asthma. Exposure to Western red cedar and, in turn,

TABLE 1.—*Selected workers at risk for occupational asthma caused by high-molecular-weight compounds*

Occupations	*Etiologic exposure*
Farmers	Grain dust; grain mites
Printers	Vegetable gums
Health care workers	Latex
Textile workers	Wool
Bakers	Plant dust and fungal enzymes
Animal handlers	Urine and dander
Woodworkers/sawmill workers	Wood dusts
Postal workers/Bookbinders	Glues

TABLE 2.—*Selected workers at risk for occupational asthma caused by low-molecular-weight compounds*

Occupations	*Etiologic exposure*
Roofers/insulators	Toluene diisocyante
Paint/plastic/chemical workers	Trimellitic anhydride
Pharmaceutical workers	Antibiotics
Health care technicians	Formaldehyde, glutaraldehyde
Printers	Chromium
Textile workers	Dyes
Hard metal grinders, carpenters (construction/woodworking)	Cobalt plicatic acid (Western red cedar)

plicatic acid occurs in a variety of occupations including sawmill work, carpentry, and construction.[20–24] Another important group of low-molecular-weight compounds is the acid anhydrides. These substances can cause symptoms of immediate airway irritation as well as asthma. Trimellitic anhydryde is among the more important, widely encountered acid anhydrides in industry. Exposure to trimellitic anhydryde occurs in the production of epoxy and alkyd resins used to manufacture coating materials such as paints and plastics.[25–27] Examples of some important occupational exposures to low-molecular-weight agents that cause asthma are shown in Table 2. A more comprehensive listing may be found elsewhere.[18]

A number of findings support the concept that immunologic mechanisms play an important role in mediating asthma caused by both low- and high-molecular-weight compounds. Evidence supporting a role for the immune system includes the observation that an immunoglobulin response may be found following exposure to many of the high-molecular-weight compounds that cause asthma. Although not typical of the low-molecular-weight compounds, some of these inducers of asthma such as the acid anhydrides also promote immunoglobulin responses. Importantly, the agents implicated as etiologic in occupational asthma do not cause disease in all individuals, again suggesting that host response is an important determinant in shaping the natural history in the exposed worker. Additionally, a period of latency that may last for weeks, months, or years can be expected between initial exposure and evolution of frank asthma. Finally, once the affected individual is sensitized from initial exposures (that is, the immune system is primed), extremely low concentrations of the substance can provoke subsequent episodes of bronchospasm. For example, in the sensitized individual, toluene diisocyanate (TDI) can induce bronchospasm in concentrations as low as one part per billion.[28]

These observations underscore two very important and clinically relevant points regarding the diagnosis and management of occupational asthma. First, the latency between initial exposure and onset of symptoms means that the concept of a "new" workplace exposure must be interpreted broadly. Second, the potential for an exceptionally low-dose exposure to precipitate bronchospasm among sensitized persons typically renders personal respirators ineffective in preventing exacerbations. Instead, complete avoidance of the exposure should be encouraged, which will typically necessitate a job change. Other options that should be considered, whenever possible, include substituting a nonsensitizing material for the suspected asthma inducer or engineering controls to reduce the risk of exposure. These interventions may prevent the affected worker from having to make a major job change. They may also have the benefit of eliminating or reducing the risk of new cases of occupational asthma among other workers who are not yet symptomatic. Importantly, occupational asthma should not be viewed as an idiosyncratic response to a workplace exposure. Instead, a well-defined case of occupational asthma should be viewed as evidence of a potential health hazard in the workplace that requires modification to prevent more cases in the future.

In contrast with agents that appear to require immune system participation to cause asthma, irritant inhalant exposure in high concentrations can cause asthma through apparently nonimmunological mechanisms. Short-term, high-level exposure to irritant fumes, vapors, or smoke can cause reactive airways dysfunction syndrome (RADS). RADS refers to asthma that is caused by a single toxic inhalational exposure.[29–31] The key feature of RADS is that, by definition, the affected individual must have had a documented high-level irritant exposure, usually resulting from a single major industrial accident. Symptoms typically develop within hours of the exposure. Strictly defined, the affected individual may not have had a preexisting diagnosis of asthma or a syndrome of reversible airflow obstruction. As in other forms of asthma, exacerbations and remissions can be expected in RADS, although most people with RADS have less reversibility in their airflow obstruction compared with others with asthma.[32,33]

Occupational Triggers of Preexisting Asthma

A wide variety of occupational exposures can trigger bronchospasm among persons with preexisting asthma.

TABLE 3.—*Settings in which to suspect an occupational factor in asthma*

1. All cases of adult-onset asthma
2. Cases in which a worker suggests a link between the workplace and deterioration in respiratory health
3. Asthma that began or worsened after a job change
4. Asthma that follows a one-time high-level irritant inhalant exposure (for instance, Reactive Airways Dysfunction Syndrome)
5. Occupations with airborne exposures that can be easily seen or smelled (dust, vapors, smoke)
6. Occupations in which the worker is advised to use a personal respirator

An exposure that may trigger bronchospasm in one individual, however, may have no significant effect on airway function in others with asthma. Moreover, the intensity and duration of bronchospasm triggered by a given provocative exposure will vary among persons with asthma in ways that are not easy to explain or predict.

Gases, dust, smoke, and particles have all been shown to cause airflow limitation in people with asthma.[34] Chlorine gas is the most common irritant gas exposure encountered in industry. Workers in textile, pulp bleaching, and water purification industries may be affected.[35] Dust can be encountered in any industry that involves movement, disruption, or disintegration of either organic or inorganic materials. Dusty occupations include farming, construction, mining, and certain manufacturing procedures. Smoke is a complex mixture of gases and particulates that results from incomplete combustion. Smoke inhalation resulting from structural fires is a well-recognized cause of airflow obstruction and an obvious occupational hazard among firefighters.[36] Cigarettes are another important source of smoke exposure. Although restrictions on smoking in the workplace are becoming more widespread, they have not been universally adopted. Consequently, secondhand cigarette smoke remains a relevant noxious inhalant, particularly among indoor workers such as restaurant and bar workers and some flight attendants. Finally, inhalational exposure of very small particles in the micron and submicron range has been correlated with reductions in airflow in people with asthma.[37,38] While epidemiological investigations studying respiratory effects of particle inhalation have focused predominantly on ambient air pollutants, they do support the hypothesis that particle inhalation—whatever the source and whatever the chemical composition—may have a deleterious effect on airway function among those with asthma. That is, respirable particles may act in a nonspecific or generic manner to cause bronchospasm.

When To Consider a Diagnosis of Occupational Asthma

An occupational history should be part of the initial evaluation of all adults with asthma, including a complete work history detailing all jobs as far back in time as possible. It is important to recognize that some occupational exposures can be important, but unrecognized, triggers of bronchospasm in people who report having had asthma all their lives. In these circumstances it is easy to dismiss deterioration in respiratory function as unavoidable disease progression when, in fact, deterioration in respiratory function may be attributable to an avoidable workplace exposure. While occupational factors should be assessed in all workers with asthma, several general circumstances, delineated in Table 3, merit particularly close scrutiny. When a worker with asthma reports that one or more of these circumstances is present, the health care practitioner should suspect an occupational factor and pursue further questioning.

How to Diagnose Occupational Asthma

It is axiomatic that a diagnosis of asthma must be established before a diagnosis of occupational asthma can be considered. Moderate and severe bronchospasm is generally readily recognizable and, in those cases, the diagnosis of asthma should be established without difficulty. In cases of mild asthma, including many cases of mild, new-onset occupational asthma, disease presentation can be subtle and the diagnosis may be more elusive. Episodic dry cough, chest tightness, and increased breathing effort may be the only manifestations of asthma in some individuals. Patients may absolutely deny a history of frank shortness of breath or wheezing. Objective data from spirometry and peak flow meter recordings demonstrating airflow obstruction that reverses after the administration of a bronchodilator, or symptomatic improvement after empiric treatment with a bronchodilator, may suggest the diagnosis. A history of spontaneous improvement in respiratory symptoms or function will support a diagnosis of asthma. Additionally, a trial of avoidance to exposures such as dust, smoke, vapors, fumes, and aeroallergens followed by improvement in respiratory status is also strongly suggestive of asthma.

Confirming a diagnosis of occupational asthma and implicating a specific exposure can be challenging. No single test clinches the diagnosis. Since asthma is characterized by exacerbations and remissions, evaluation of a patient's disorder at one point in time may not fully characterize the disorder. Multiple exposures may be relevant, both in and out of the workplace, further complicating the evaluation. Exposure–response intervals that last many hours may complicate recognition of occupational asthma. Specific airway challenges with suspected agents in an exposure laboratory, although appealing in principle, are not widely available or validated. Moreover, they are complicated and cannot fully replicate real-world exposure settings.[39] As a consequence, their use remains largely confined to research. In the end, a preponderance of evidence must be viewed as the clinical gold standard for the diagnosis of occupational asthma in most clinical practices. The diagnosis will generally be established from a detailed history supported by serial lung function studies.

TABLE 4.—*Questions to determine links between the workplace and asthma symptoms*

1. Is there a diurnal temporal relationship between work and the onset of bronchospasm? In other words, do symptoms develop in a predictable manner, either during or after exposures at work or after returning home from work on days with exposure?
2. Do symptoms improve during vacations, over the weekend, or during any other extended period away from work?
3. Are symptoms worse at the end of the workweek?

TABLE 5.—*Questions to assess the job process*

1. In as much detail as you can provide, what do you do?
2. Do you have a Material Safety Data Sheet in your workplace? (If yes, obtain a copy.)
3. Can you see particles or dust in the air at work?
4. Do you blow dust out of your nose or cough up dust at the end of the workday?
5. Are you exposed to vapors, fumes, mists, or chemicals?
6. Are you advised to wear a personal respirator? Have you been personally fitted for one? Do you wear it faithfully?
7. (With worker concurrence only) To the employer or employer safety and health personnel: Please provide any information about industrial hygiene surveys, workplace illness surveillance and monitoring, the presence of other affected workers (current or past), and the presence of any known asthma sensitizers or irritants in the workplace.

Since occupational asthma is, in the end, a clinical diagnosis, the accuracy of the diagnosis and the efficacy of the management that follows from the diagnosis will depend heavily on the quality and availability of relevant data. Moreover, the consequences of a false-positive versus a false-negative diagnosis of occupational asthma for a given worker will necessarily have an impact on data interpretation and, accordingly, the management of that worker. Inevitably, real-world issues, including the economic consequences to the patient and the employer, will influence prevention and treatment strategies.

At a minimum, the history should address each of the six special circumstances detailed in Table 3. Other important questions which address the temporal relationship between symptoms and work may help to establish an exposure–response relationship between the workplace and bronchospasm (Table 4). Even though these classic exposure–response temporal relationships are often present early in the course of illness, they may not be apparent later in the course, thereby complicating diagnosis.

It is important to note that specific preformed IgE bound to mast cells mediates asthma caused by many high-molecular-weight compounds. Exposure to these high-molecular-weight compounds can, in the sensitized person, provoke an immediate response, or early-onset asthma. Peak symptoms will often occur within 30 minutes of exposure.[3] In contrast, low-molecular-weight compounds may cause late-onset occupational asthma symptoms that may not develop until 4–6 hours after exposure, with peak symptoms developing 8–10 hours after exposure.[3] Finally, both low- and high-molecular-weight compounds can cause a dual response, with features of both early- and late-onset asthma. In any case, diurnal patterns of bronchospasm related to workplace exposure should suggest occupational asthma.

Details about the job process may suggest relevant occupational exposures. A job title, by itself, rarely provides a complete picture of the work task. A series of questions (listed in Table 5) can provide circumstantial evidence linking the workplace with respiratory symptoms. The worker should be instructed to obtain information about hazardous materials in the workplace. The Occupational Safety and Health Administration requires employers to make Material Safety Data Sheets (MSDS) readily available to workers. These documents provide a detailed list of hazardous materials in the workplace and their potential toxicities, including respiratory effects. The Chemical Manufacturers' Association CHEMTREC can also provide assistance in obtaining chemical specific information (1-800-262-8200). MSDSs should not be viewed as the sole reference for possible exposures that can cause or trigger asthma. With the approval of the worker, communication with the employer regarding workplace materials and existing environmental surveys can be an additional source of information regarding possible important exposures.

Another valuable resource is the National Institute for Occupational Safety and Health (NIOSH) which provides, by telephone or Internet, a wide variety of information on worker health, including occupational respiratory disorders (1-800-356-4674; http://www.cdc.gov/niosh/homepage.html). Exposure assessment and diagnostic strategies have also been described in a recent consensus statement published by the American College of Chest Physicians.[40]

There are no physical examination findings that are specific for occupational asthma. Skin testing may establish whether an individual is sensitized to a specific antigen. A substance that produces a positive wheal and flare on skin testing, however, may not necessarily be a cause or trigger of asthma in a given worker. Further, immunologic testing is, with a few exceptions, useless in testing for sensitization to low-molecular-weight compounds.

After the history and physical examination, repeated pulmonary function testing is the most important tool in diagnosing occupational asthma. Any objective data about lung function predating a work exposure suspected of causing or exacerbating asthma can provide valuable baseline data. Typically, however, in the previously asymptomatic individual, lung function studies will never have been performed. Serial peak expiratory flow monitoring with a handheld ambulatory meter or spirometry demonstrating changes in airflow temporally related to work support a diagnosis of occupational asthma. Examples of peak expiratory flow rate monitors are shown in Fig. 1. Diurnal variability of 20% or greater in peak flow

Figure 1.—Ambulatory peak expiratory flow rate monitoring. Measurement of peak expiratory flow rate every 2 hours for a 2-week period at work and away from work provides objective data that can support a diagnosis of occupational asthma. A. Examples of peak flow meters: TruZone, Monaghan Medical Corp (Plattsburgh, NY) (left) and Personal Best, HealthScan Products, (Cedar Grove, NJ) (right). B. Proper technique for measuring peak expiratory flow: upright position; firm seal around the mouthpiece; lungs filled completely at the beginning of the maneuver. The forced expiratory maneuver is performed as hard and fast as possible. The greatest of three consecutive maneuvers is recorded.

indicates abnormal changes in airflow over short periods of time consistent with asthma.[41] Peak expiratory flows should be recorded every 2 hours while awake on work days and ideally for a 2-week period away from work.[39,40,42,43] Importantly, in those individuals who demonstrate a late asthmatic response, decrements in lung function may be most pronounced hours after they have left the workplace. Documentation of clear improvement in lung function after prolonged absence from the workplace, such as after vacations, is very strong evidence for an occupational exposure factor.

Occupational asthma ultimately remains a clinical diagnosis. The diagnosis is supported by a focused evaluation that should establish a history of workplace exposure to a recognized noxious agent. Temporal links between a relevant occupational exposure and both asthma symptoms and airflow obstruction provide strong additional support for the diagnosis.

Prevention, Treatment, and Legal Implications

Prevention is the cornerstone of management of occupational asthma. If a preponderance of evidence supports a link between the workplace and asthma, then measures should be advocated to modify the worksite or remove the worker from the exposure setting. The primary effort should be to modify the workplace to prevent continued exposure. Since one case of occupational asthma may presage others, workplace modifications may have beneficial effects that extend beyond the symptomatic worker. Specifically, workplace modifications may prevent the evolution of illness in other workers who have not yet experienced symptoms or significant loss of lung function. In some cases, however, the worker will need to change job tasks. It is the obligation of physicians to report cases of occupational asthma to state and/or county health boards under the OSHA act of 1970. More information on industrial hygiene issues can be found at the OSHA web site (http://www.osha.gov/wutsnew.html).

Early removal of the worker from the suspected exposure has important prognostic implications. Multiple studies have demonstrated that asthma symptoms linked to a workplace exposure may persist years after removal from the exposure.[44–46] Studies have also shown that early diagnosis of occupational asthma and early removal from an inciting exposure are important in regaining lung function and controlling symptoms.[47–50]

Usual asthma therapies may be used in managing asthma resulting from occupational exposures. These include beta-2–specific adrenergic agonists, corticosteroids, and adjuvant anti-inflammatory medications. A stepwise approach to the use of asthma medications and to

asthma management was well delineated in a monograph recently produced by the National Institutes of Health National Asthma Education and Prevention Program.[41] Bronchodilators and other asthma medications should never substitute for preventive measures, however.

The use of masks to provide respiratory protection is usually not an effective intervention and should not be viewed as a substitute for workplace modification or removal of the worker from the exposure setting. For example, among workers with TDI-induced asthma, continued occasional exposure to TDI has been demonstrated to cause progressive deterioration in lung function and bronchial hyperresponsiveness despite the use of respiratory protection compared with workers who were no longer exposed.[51] Since low-molecular-weight compounds such as TDI can induce bronchospasm after exposure to concentrations as low as one part per billion,[28] it is unreasonable to expect satisfactory protection from a mask.

In cases of asthma triggered by high-dose irritant exposure, such as nuisance dusts, respiratory protection with masks may be a reasonable second-line management strategy if the worker cannot or will not leave the job. This management strategy presumes that most irritants trigger bronchospasm in a dose-dependent manner through nonallergic mechanisms. Such a dose-response relationship has been reported among boilermakers exposed to fuel ash, a particulate generated from fossil fuel combustion. Hauser et al[52] reported the results of a prospective evaluation in which they showed a significant dose-response relationship between the decline in the adjusted change in airflow and the peak and average particulate exposure during a 4-week period. Nevertheless, despite the fact that a reduction in nuisance dust and irritant exposures afforded by respiratory protection masks may have a salutary health effect among people with asthma, complete avoidance of triggers should remain the principle management goal.

Disease surveillance is an essential component in the prevention of occupational asthma. In a recent discussion of strategies to prevent occupational asthma, Venables[53] highlighted the importance of surveillance to gain information on how common asthma is relative to other occupational lung diseases and on the relative frequency with which different agents cause asthma. Occupational safety and health is one of the priority areas targeted in the US Department of Health and Human Services report, "Healthy People 2000."[54] In the United States, the Sentinel Event Notification System for Occupational Risks (SENSOR), in collaboration with NIOSH, has been developed as a national program for occupational disease surveillance, including occupational asthma.[55] The program involves collaboration between NIOSH and state and county health departments. The surveillance case definition used by NIOSH is inclusive and includes all cases of asthma caused by or aggravated by workplace exposures.[56] A classification scheme using the overarching term "work-related asthma" has been proposed as part of planned report of findings from SENSOR-participating states. Surveillance case definitions are currently in development for this report, but both new-onset and work-aggravated asthma will be included (written communication; Ruth Jajosky, DMD, MPH; NIOSH). Finally, physician-filed workers' compensation reports are, in some US states, a very important and reliable source of surveillance and are accessed in the SENSOR program.

It is important to recognize that workers can be compensated for asthma that is caused by or aggravated by an occupational exposure. While impairment must be demonstrated, it is not necessary to prove that asthma was entirely caused by an occupational factor to meet eligibility requirements for disability compensation. Claim disputes may arise with regard to the work-relatedness of the worker's asthma and the extent of disability. In the United States, claim disputes are generally resolved by litigation through a court-administered system or a wholly administrative system.

Under a wholly administrative system, workers' compensation boards, which are part of the Department of Labor but consist of members chosen by both employers and employees, review claims. When a claim is accepted, complete medical care is provided and paid for by either private insurance or a state compensation fund.[57]

An estimated 60% to 90% of those with documented occupational asthma continue to demonstrate respiratory impairment after leaving an exposure.[58] Accordingly, workers may be entitled to compensation for work-related disability. Disability is different from impairment. Impairment is defined as a functional abnormality resulting from a medical condition. It may be temporary or permanent. Disability indicates the total effect of impairment on the individual and will depend on the job and the worker's ability to compete in an open job market. Impairment is determined by the physician, and disability is determined by disability raters, workers' compensation judges, and review boards.

Guidelines for determining impairment due to asthma have been developed by the American Thoracic Society.[59] The guidelines use a scoring system consisting of several physiologic and clinical parameters to characterize impairment: *1*) postbronchodilator forced expiratory volume in 1 second (FEV_1) measured by spirometry, *2*) reversibility of FEV_1 or degree of airway hyperresponsiveness, and *3*) minimum asthma medication need. Recovery from occupational asthma may continue for as long as 2 years after removal from an exposure.[19] Accordingly, assessment for long-term impairment and disability should be carried out 2 years after the removal from an exposure, at which time improvement can be expected to have reached a plateau.

In summary, occupational asthma is a prevalent disorder caused by a wide variety of respirable exposures including organic and inorganic compounds. A diagnosis of occupational asthma will only be established if there is suspicion that asthma symptoms may be causally linked to the workplace. The diagnosis is clinically based and is supported by evidence gained from a detailed and focused history and pulmonary function

testing, including ambulatory peak expiratory flow monitoring. Material Safety Data Sheets and other sources provide worksite-specific information about hazardous exposures and may be useful in identifying a specific etiologic exposure. The cornerstone of management is prevention, which typically mandates a change in the work environment or significant work task modifications. Workers with occupational asthma are entitled to compensation, including disability compensation for workers with evidence of persistent impairment after removal from the workplace exposure. Claims disputes are usually settled through litigation.

Acknowledgment

The authors gratefully acknowledge James Canfield's assistance with preparation of the figure.

REFERENCES

1. Adams PF, Marano MA. Current estimates from the National Health Interview Survey, 1994. Vital Health Stat 1995; 10:94

2. Weiss KB, Gergen PJ, Hodgson TA. An economic evaluation of asthma in the United States. N Engl J Med 1992; 326:862–866

3. Venables KM, Chan-Yeung M. Occupational asthma. Lancet 1997; 349:1465–1469

4. Kogevinas M, Anto JM, Sorian JB, Tobias A, Burney P, the Spanish Group of the European Asthma Study. The risk of asthma attributable to occupational exposures: a population-based study in Spain. Am J Respir Crit Care Med 1996; 154:137–143

5. Ameille J, Pairon JC, Bayeux MC, et al. Consequences of occupational asthma on employment and financial status: a follow-up study. Eur Respir J 1997; 10:55–58

6. Gannon PFG, Weir DC, Robertson AS, Burge PS. Health employment and financial outcomes in workers with occupational asthma. Br J Ind Med 1993; 50:491–496.

7. Blanc PD, Jones M, Besson C, Katz P, Yelin E. Work disability among adults with asthma. Chest 1993; 104:1371–1377

8. Kahan E, Wiengarten MA, Appelbaum T. Attitudes of primary care physicians to the management of asthma and their perception of its relationship to patients' work. Isr J Med Sci 1996; 32:757–762

9. Gannon PF, Bright P, Campbell M, O'Hickey SP, Burge PS. Occupational asthma due to glutaraldehyde and formaldehyde in endoscopy and x ray departments. Thorax 1995; 50:156–159

10. Newman-Taylor AJ. Occupational asthma. Thorax 1980; 35:241–245

11. Cartier A. Definition and diagnosis of occupational asthma. Eur Respir J 1994; 7:153–160

12. Wagner GR, Wegman DH. Occupational asthma: prevention by definition. Am J Ind Med 1998; 33:427–429

13. Wheeler S, Rosenstock L, Barnhart S. A case series of 71 patients referred to a hospital-based occupational and environmental medicine clinic for occupational asthma. West J Med 1998; 168:98–104

14. Tarlo SM, Liss G, Corey P, Broder I. A workers' compensation claim population for occupational asthma: a comparison of subgroups. Chest 1995; 107:634–641

15. Harber P. Assessing occupational disability from asthma. J Occup Med 1992; 34:120–128

16. Chan-Yeung M, Malo J. Etiologic agents in occupational asthma. Eur Respir J 1994; 7:346–371

17. Cote J, Kennedy S, Chan-Yeung M. Outcome of patients with cedar asthma with continuous exposure. Am Rev Respir Dis 1990; 141:373–376

18. Malo JL, Cartier A. Key references in occupational asthma. Appendix B. In Harber P, Schneker M, Balmes J (Eds): Occupational and Environmental Respiratory Disease. St. Louis, Mosby, pp 1006–1022

19. Malo J-L, Cartier A, Ghezzo H, Lafrance M, McCants M, Lehrer SB. Patterns of improvement on spirometry, bronchial hyperresponsiveness, and specific Ig E antibody levels after cessation of exposure in occupational asthma caused by snow-crab processing. Am Rev Respir Dis 1988; 138:807–812

20. Cote J, Kennedy S, Chan-Yeung M. Outcome of patients with cedar asthma with continuous exposure. Am Rev Respir Dis 1990; 141:373–376

21. Noertjojo HK, Dimich-Ward H, Peelen S, Dittrick M, Kennedy SM, Chan-Yeung M. Western red cedar dust exposure and lung function: a dose-response relationship. Am J Respir Crit Care Med 1996; 154:968–973

22. Chan-Yeung M, Chan H, Salari H, Lam S. Histamine and leukotrienes release in bronchial fluid during plicatic acid-induced bronchoconstriction. J Allergy Clin Immunol 1989; 84:762–768

23. Lin FJ, Dimich-Ward H, Chan-Yeung M. Longitudinal decline in lung function in patients with occupational asthma due to western red cedar. Occup Environ Med 1996; 53:753–756

24. Chan-Yeung M. Mechanism of occupational asthma due to western red cedar (*Thuja plicata*). Am J Ind Med 1994; 25:13–18

25. Grammer LC, Shaughnessy MA, Zeiss CR, Greenberger PA, Patterson R. Review of trimellitic anhydride (TMA) induced respiratory response. Allergy Asthma Proc 1997; 18:235–237

26. Cui ZH, Sjostrand M, Pullerits T, Andius P, Skoogh BE, Lotwall J. Bronchial hyperresponsiveness, epithelial damage, and airway eosinophilia after single and repeated allergen exposure in a rat model anhydride-induced asthma. Allergy 1997; 52:739–746

27. van Tongeren MJ, Barker RD, Gardiner K, Harris JM, Venables KM, Taylor AJ, et al. Exposure to acid anhydrides in three resin and one cushioned flooring manufacturing plants. Ann Occup Hyg 1995; 39:559–571

28. Henschler D, Assman W, Meyer KO. The toxicology of toluene di-isocyanate. Archs Toxicol 1962; 19:364–387

29. Brooks SM, Weiss MA, Bernstein IL. Reactive airways dysfunction syndrome. Case reports of persistent airways hyperreactivity following high-level irritant exposures. J Occup Med 1985; 27: 473–476

30. Alberts WM, do Pico GA. Reactive airways dysfunction syndrome. Chest 1996; 109:1618–1626

31. Taylor AJN. Respiratory irritants encountered at work. Thorax 1996; 51:541–545

32. Bherer L, Cushman R, Courteau JP, Quevillon M, Cote G, Bourbeau J, et al. A survey of construction workers repeatedly exposed to chlorine over a 3-6 month period in a pulpmill. II. Follow-up of affected workers with questionnaire, spirometry and assessment of bronchial responsiveness 18 to 24 months after exposure ended. Occup Environ Med 1994; 51:225–228

33. Gautrin D, Boulet LP, Boutet M, Dugas M, Bherer L, L'Archeveque J. Is reactive airways dysfunction syndrome (RADS) a variant of occupational asthma? J Allergy Clin Immunol 1994; 93:12–22

34. Kuschner WG, Blanc PD. Gases and other inhalants. In LaDou J (Ed): Occupational and Environmental Medicine, 2nd ed. Stamford, Conn, Appleton & Lange, 1997, pp 571–583

35. Das R, Blanc PD. Chlorine gas exposure and the lung: a review. Toxicol Ind Health 1993; 9:439–455

36. Unger KM, Snow RM, Testas JM, Miller WC. Smoke inhalation in firemen. Thorax 1980; 356:838–842

37. Peters A, Wichmann HE, Tuch T, Heinrich J, Heyder J. Respiratory effects are associated with the number of ultrafine particles. Am J Respir Crit Care Med 1997; 155:1376–1383

38. Pope CA III. Respiratory disease associated with community air pollution and a steel mill, Utah Valley. Am J Public Health 1989; 79:623–628

39. Godnic-Cvar J. How to confirm occupational asthma. Int Arch Occup Environ Health 1995; 67:79–84

40. Chan-Yeung M. Assessment of asthma in the workplace. ACCP consensus statement; American College of Chest Physicians. Chest 1995; 108:1084–1117

41. National Asthma Education and Prevention Program. Highlights of the Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma. NIH publication no. 97-4051A, Bethesda, MD, 1997

42. Gannon PF, Burge PS. Serial peak expiratory flow measurement in the diagnosis of occupational asthma. Eur Respir J 1997; 24:57S–63S

43. Gannon PF, Newton DT, Belcher J, Pantin CF, Burge PS. Development of OASYS-2: a system for the analysis of serial measurement of peak expiratory flow in workers with suspected occupational asthma. Thorax 1996; 51:484–489

44. Chan-Yeung M, MacLean L, Paggiaro PL. Follow up study of 232 patients with occupational asthma caused by western red cedar (*Thuja plicata*). J Allergy Clin Immunol 1987; 79:792–796

45. Lozewicz S, Assoufi BK, Hawkins R, Newman Taylor AJ. Outcome of asthma induced by isocyanate. Br J Dis Chest 1987; 81:14–22

46. Paggiaro PL, Loy AM, Rossi O, Ferrante B, Pardi F, Roselli MG, Bascheiri L. Follow up study of patients with respiratory disease due to toluene diisocyante (TDI). Clin Allergy 1984; 14:463–469

47. Pisati G, Zedda S. Outcome of occupational asthma due to cobalt hypersensitivity. Sci Total Environ 1994; 150:167–171

48. Lin FJ, Dimich-Ward J, Chan-Yeung M. Longitudinal decline in lung function in patients with occupational asthma due to western red cedar. Occup Environ Med 1996; 53:753–758

49. Soyseth V, Kongerud J, Kjuus J, Boe J. Bronchial responsiveness and decline in FEV1 in aluminum potroom workers. Eur Respir J 1994; 7:888–894

50. Noertjojo HK, Dimich-Ward J, Peelen S, Dittrick M, Kennedy SM, Chan-Yeung M. Western red cedar dust exposure and lung function: a dose-response relationship. Am J Respir Crit Care Med 1996; 154:968–973

51. Pisati G, Baruffini A, Sedda S. Toluene diisocyante induced asthma: outcome according to persistence of cessation of exposure. Br J Ind Med 1993; 50:60–64

52. Hauser R, Elreedy S, Hoppin JA, Christiani DC. Airway obstruction in boilermakers exposed to fuel oil ash: a prospective investigation. Am J Respir Crit Care Med 1995; 152:1478–1484

53. Venables KM. Prevention of occupational asthma. Eur Respir J 1994; 7:768–778

54. Public Health Service. Healthy people 2000: national health promotion and disease prevention objectives. Washington, DC, US Department of Health and Human Services, Public Health Service, 1990, DHHS publication no. (PHS)90-50212

55. Matte TD, Hoffman RE, Rosenman KD, Stanbury M. Surveillance of occupational asthma under the SENSOR model. Chest 1990; 98(Suppl 5): 173S–178S

56. Klees JE, Alexander MA, Rempel D, Beckett W, Rubin R, Barnhart S, et al. Evaluation of a proposed NIOSH surveillance: case definition for occupational asthma. Chest 1990; 98(Suppl 5):212S–215S

57. Seligman PJ, Bernstein IL. Medicolegal and compensation aspects. In Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI (Eds): Asthma in the Workplace. New York, Marcel Dekker, 1993, pp 323–340

58. Chan-Yeung M. State of the art—occupational asthma. Chest 1990; 98:148S–161S

59. American Thoracic Society. Guidelines for the evaluation of impairment/disability in patients with asthma. Am Rev Respir Dis 1993; 147: 1056–1061

Articles

Controversies in Perioperative Medicine

HUGO QUINNY CHENG, MD, *San Francisco, California*

Coexisting medical problems are common in surgical patients. Due to the lack of convincing studies, however, the optimal strategies for perioperative management of many medical problems remain unclear. Thus, practices are often based on inconclusive clinical studies or extrapolated from current understanding of pathophysiology. This article reviews guidelines and practices for endocarditis prophylaxis, perioperative anticoagulation in patients with mechanical heart valves, glucose control in diabetic patients undergoing surgery, and the use of β-blockers to prevent postoperative cardiac complications. In addition, the strength of the evidence supporting these practices is evaluated.

(Cheng HQ. Controversies in perioperative medicine. West J Med 1998; 169:351–355)

Endocarditis Prophylaxis

Many invasive procedures induce transient bacteremia. Normal cardiac endothelium resists bacterial colonization. Some cardiac abnormalities, however, increase the risk of colonization and development of bacterial endocarditis. Thus, it has become standard practice to administer prophylactic antibiotics to patients with certain cardiac conditions when they undergo procedures likely to cause bacteremia. Rates of bacteremia are highest after dental work and other procedures involving the oropharynx.[1] Endocarditis originating from such procedures is usually due to α-hemolytic (*viridans*) *Streptococci* spp. Genitourinary and gastrointestinal procedures also frequently cause bacteremia. *Enterococcus* spp. is the organism most likely to cause endocarditis after such procedures.

In 1997, the American Heart Association issued its most recent guidelines for endocarditis prophylaxis.[2] It recommends prophylactic antibiotics only for patients with a moderate- or high-risk cardiac abnormality (Table 1) undergoing a high-risk procedure (Table 2). Antibiotic regimens have been simplified (Table 3). For oral and upper-airway procedures, the dose of amoxicillin has been reduced, and a follow-up dose is no longer recommended. Because antibiotic resistance is often encountered with enterococci, the combination of ampicillin and gentamicin is still recommended for patients with high-risk cardiac abnormalities. Amoxicillin alone, however, is now deemed acceptable for patients with moderate-risk abnormalities.

The utility of endocarditis prophylaxis is uncertain. A Dutch study found that only 1 in 10 patients with endocarditis had recently undergone a procedure for which prophylaxis was recommended.[3] Thus, even universal adherence to recommendations is likely to prevent only a few cases of endocarditis, because most cases are not iatrogenic. This is not surprising, given that bacteremia follows many routine nonmedical activities. For instance, the frequency of bacteremia from routine tooth brushing (estimated at 40%) approaches that from tooth extraction (60%).[1]

No prospective study has evaluated the efficacy of endocarditis prophylaxis. A retrospective cohort study of 533 patients with prosthetic valves showed a significant reduction in the risk of endocarditis among those who received prophylactic antibiotics.[4] Two case-control studies arrived at conflicting conclusions. One claimed that prophylaxis was 91% effective at preventing postdental endocarditis.[5] The study included only eight cases, however, including two cases of culture-negative disease and two in which the diagnosis of endocarditis was made more than 2 months after the dental procedure. Misclassification of cases was thus likely. A case-control study examining 48 patients with native valve endocarditis showed no benefit to prophylaxis.[6]

Further consideration must be given to the risks and costs of prophylaxis. A decision analysis of using penicillin prophylaxis in patients with mitral valve prolapse (based on older guidelines) concluded that parenteral penicillin would lead to a net loss of life due to anaphylactic reactions.[7] Prophylaxis with oral penicillin spared life in the analysis, but only in older patients and at a cost of more than $1 million per year of life saved.

The benefits of antibiotic prophylaxis are greatest for patients with high-risk cardiac abnormalities such as prosthetic valves or prior endocarditis. For patients with moderate-risk cardiac abnormalities, the net utility is probably marginal at best. Nevertheless, given the

From the Division of General Internal Medicine, School of Medicine, University of California, San Francisco, California.

Reprint requests to H.Q. Cheng, MD, UCSF School of Medicine, Division of General Internal Medicine, 400 Parnassus Ave, A-405, San Francisco, CA 94143-0320. E-mail: quinny@medicine.ucsf.edu

TABLE 1.—*Prevention of Bacterial Endocarditis (based on the 1997 American Heart Association recommendations)*

Cardiac Abnormality and Risk of Endocarditis
Prophylaxis Recommended
High Risk
Prosthetic valves, including bioprostheses
Previous endocarditis
Surgically created systemic pulmonary shunts
Complex cyanotic congenital heart defects
Moderate Risk
Most other congenital heart defects
Acquired valve dysfunction
Hypertrophic cardiomyopathy
Mitral valve prolapse with regurgitation
Prophylaxis Not Recommended
Isolated secundum atrial septal defect
Atrial septal defect, ventricular septal defect, or patent ductus arteriosus repaired at least 6 months previously without residua
Coronary artery bypass grafts, pacemaker, implanted defibrillator
Mitral valve prolapse without regurgitation
Physiologic or functional murmurs
Rheumatic fever or Kawasaki's disease without valve dysfunction

TABLE 2.—*Prevention of Bacterial Endocarditis (based on the 1997 American Heart Association recommendations)*

Procedure and Risk of Endocarditis
Prophylaxis Recommended
Dental extraction
Periodontal procedures including surgery and scaling
Intraligamentary local anesthetic injection
Prophylactic cleanings where bleeding is anticipated
Tonsillectomy and adenoidectomy
Rigid bronchoscopy
Surgery involving respiratory mucosa
Esophageal sclerotherapy or dilatation
Endoscopic retrograde cholangiography with biliary obstruction
Biliary tract surgery
Surgery involving intestinal mucosa
Prostate surgery
Cystoscopy or urethral dilatation
Prophylaxis Not Recommended
Restorative dentistry
Nonintraligamentary anesthetic injection
Shedding of primary teeth
Endotracheal intubation
Flexible bronchoscopy*
Tympanostomy tube placement
Cardiac catheterization or pacemaker placement
Incisions or biopsy of sterilized skin
Gastrointestinal endoscopy, including biopsies and transesophageal echocardiography *
Vaginal hysterectomy*
Vaginal* or Cesarean delivery
In absence of infection: urethral catheterization, dilatation, or curettage, sterilization, therapeutic abortion, IUD manipulation

*Prophylaxis is optional in the presence of a high-risk lesion.

current medical-legal environment, the physician should offer prophylaxis according to American Heart Association guidelines, with the understanding that efficacy of prophylaxis remains unproven.

Perioperative Anticoagulation for Patients With Mechanical Heart Valves

Patients with mechanical valve prostheses generally require anticoagulation with warfarin to prevent embolic strokes and valve thrombosis. For minor procedures such as skin biopsy, cataract surgery, and dental extraction, anticoagulation can be safely continued through the perioperative period. For more invasive surgery, anticoagulation must be temporarily discontinued to prevent hemorrhagic complications. The optimal strategy for managing perioperative anticoagulation to minimize both thromboembolic and hemorrhagic complications is the subject of debate.

The most aggressive approach uses a perioperative heparin infusion while oral anticoagulation is discontinued (Table 4). This technique theoretically minimizes the risk of thromboembolic complications by keeping the patient anticoagulated for the longest possible period; however, it generally entails several days of hospitalization both before and after surgery while the patient is maintained on intravenous heparin. There may also be an increased risk of hemorrhage with aggressive anticoagulation. The opposite strategy is to withhold perioperative heparin (except as indicated for prevention of deep venous thrombosis) and make admission and discharge decisions without considering the patient's level of anticoagulation (Table 4). This practice is likely to be less costly but potentially increases the risk of thromboembolic complications.

Deciding between these dichotomous strategies requires understanding the incidence of thromboembolic complications in patients with mechanical valves while on and off warfarin. In a 1994 meta-analysis, ~4% of all patients with a mechanical aortic or mitral valve prosthesis suffered a major embolic complication each year if they were not anticoagulated.[8] Another 1.8% of such patients experienced valve thrombosis each year without anticoagulation. The annual rates for embolism and valve thrombosis were reduced to 1% and 0.2%, respectively, in patients anticoagulated with warfarin. Based on these data, discontinuing anticoagulation for 1 day confers only a 0.016% (1.6 in 10,000) risk of major embolism or valve thrombosis. This estimate assumes a linear risk over the course of 1 year. The actual risk may be further reduced due to partial anticoagulation during the time warfarin is withheld. On the other hand, a theoretical hypercoagulable state caused by discontinuing warfarin may raise the actual risk.

TABLE 3.—*Prevention of Bacterial Endocarditis (based on the 1997 American Heart Association recommendations)*

Prophylactic Regimens
Dental, Esophageal, and Upper Respiratory Tract Procedures
Standard Regimen
Amoxicillin, 2 g PO 1 hour before procedure
Options for Patients Allergic to Penicillin
Cephalexin or cefadroxil, 2 g PO 1 hour before procedure
Clindamycin, 600 mg PO 1 hour before procedure
Azithromycin or clarithromycin, 500 mg PO 1 hour before procedure
Parenteral Alternatives (for patients unable to take oral antibiotics)
Ampicillin, 2 g IV or IM within 30 minutes of procedure
Clindamycin, 600 mg IV or IM within 30 minutes of procedure
Cefazolin, 1 g IV or IM within 30 minutes of procedure
Gastrointestinal or Genitourinary Tract Procedures
High Risk Patients
Ampicillin, 2 g IV or IM, plus gentamicin, 1.5 mg/kg (≤120 mg), within 30 minutes of procedure, followed in 6 hours by ampicillin, 1 g IV or IM, or amoxicillin, 1 g PO
High Risk and Allergic to Penicillin
Vancomycin, 1 g IV (slow infusion), plus gentamicin, 1.5 mg/kg (≤120 mg); complete infusion within 30 minutes of procedure
Moderate Risk
Amoxicillin, 2 g PO 1 hour before procedure
Ampicillin, 2 g IV or IM within 30 minutes of procedure
Vancomycin, 1 g IV (slow infusion); complete infusion within 30 minutes of procedure

TABLE 4.—*Two Approaches to Managing Perioperative Anticoagulation in Patients With Mechanical Valve Prostheses*

Perioperative Heparinization ("aggressive" approach)
Stop warfarin 4 days before surgery
Admit patient 3 days before surgery
Begin intravenous heparin when International Normalized Ratio (INR) <2.5
Stop heparin 6 hours before surgery
Restart heparin and warfarin when bleeding risk acceptable
Stop heparin and consider discharging patient when INR >2.5
No Perioperative Heparinization ("minimalist" approach)
Stop warfarin 4 days before surgery
Admit patient at usual time (check INR before surgery)
Restart warfarin when bleeding risk acceptable
Discharge patient without regard to INR

The study also found that the position and design of the prosthesis altered the incidence of thromboembolism. An aortic valve prosthesis conferred approximately half the thromboembolism risk of a prosthetic mitral valve. Newer valve designs (tilting disk and bileaflet) were found to be less thrombogenic than older caged-ball valves. Risk of major embolism was reduced by 30% to 40% with the newer valve designs. Thus, the estimated risk of thromboembolism off warfarin would be even lower in patients with a modern valve prosthesis, especially if the prosthesis were placed in the aortic position.

The risk and cost of perioperative heparinization must also be considered. A recent decision analysis concluded that perioperative heparin infusion marginally increases mortality and disability because bleeding risks outweigh the risk of thromboembolism.[9] A similar conclusion was reached for patients anticoagulated for atrial fibrillation or recurrent venous thrombosis. An earlier cost-benefit analysis estimated that the first "extra" day of hospitalization for the sole purpose of heparinization would cost $2 million per death averted.[10]

Data from observational studies support withholding perioperative heparin in some patients with prosthetic valves. Three case series published in the late 1970s found no postoperative thromboembolic events in more than 100 patients with isolated aortic prostheses managed without heparin.[11–13] The vast majority of these patients had the more thrombogenic caged-ball valves. For patients with mitral valves, the data are less clear. One small series reported two major perioperative thromboembolic events in 10 patients managed without heparin.[11] A larger series, however, found no such complications in 74 patients with mitral prosthesis, the majority of whom received no perioperative anticoagulation.[13]

Based on available data, routine perioperative heparinization for patients with aortic valve prostheses seems unjustified. A mechanical mitral valve incurs a greater risk of thromboembolism. Thus, heparinization should be considered for patients with mitral prostheses, particularly those who have older valve designs. It remains to be seen how low-molecular-weight heparin, which can be administered at home, will affect practice.

Perioperative Glucose Control in Diabetes

Diabetic patients have an increased risk of surgical wound complications, particularly wound infections.[14] A prospective study found an overall infection rate of 1.8% for "clean" wounds; among diabetic patients, however, the infection rate was 10.7%. The reason for the increased risk of wound infection is unclear. If hyperglycemia directly promotes wound infection, then tighter perioperative glucose control should be beneficial. If chronic diabetic complications such as vasculopathy and neuropathy are the major contributors, then aggressive perioperative glucose control would have little effect on wound healing. A strategy of tight control in that case would needlessly increase the risk of hypoglycemia, especially in surgical patients with erratic and unpredictable diets.

Most proponents of tighter perioperative glucose control cite *in vitro* and animal studies that demonstrate adverse effects of hyperglycemia. Neutrophils taken from poorly controlled diabetic patients have diminished chemotactic and phagocytic activity.[15] Neutrophil function in those patients was restored by improving the subjects' glucose control. An animal model of type 2

diabetes can be created with the drug streptozotocin, which induces a state of nonketotic hyperglycemia in rats. Surgical wounds in the hyperglycemic rats have decreased tensile strength and lower collagen content than wounds in normal rats.[16] Wound strength could be improved if the hyperglycemic rats were treated with frequent insulin injections. The clinical relevance of these findings remains uncertain.

No randomized trials have been done on the effects of perioperative glucose control on wound complication rates. One retrospective study examined the effects of a diabetes control protocol on the rate of deep wound infections in diabetic patients undergoing open heart surgery.[17] The protocol used a postoperative intravenous insulin infusion titrated to keep blood glucose under 200 mg/dl. The incidence of deep wound infection after implementation of the protocol was significantly lower than in the preprotocol era. Furthermore, the investigators found a direct correlation between average blood glucose on the first postoperative day and rate of deep wound infection.

The study, however, fails to definitively prove that tighter glycemic control prevents wound infection in diabetes. The study period spanned 7 years. It is unclear what other changes in surgical and postoperative care were made during the study period that could have prevented infections. Furthermore, the positive correlation between postoperative glucose levels and infection rate does not imply causation. Severe postoperative hyperglycemia may be simply a marker for patients with more severe diabetes. Such patients are likely to have more chronic diabetic complications, which may be the actual cause of the high infection rate.

Another controversy in perioperative diabetes management concerns the optimal regimen to achieve glycemic control. Diabetic patients controlled by diet alone usually can be managed with sliding-scale subcutaneous insulin. Oral hypoglycemic agents must be discontinued in fasting patients because such drugs have prolonged action and may cause hypoglycemia. Again, subcutaneously administered insulin is generally recommended to maintain relative euglycemia perioperatively in patients managed with oral hypoglycemic agents. For type 1 and type 2 diabetes maintained on insulin, perioperative insulin is usually required. Traditionally, one-half to two-thirds of the patient's long-acting insulin is administered on the morning of surgery, and a glucose infusion is started. Additional adjustments to the patient's serum glucose are made with a subcutaneous insulin sliding scale. Many diabetologists, however, argue that perioperative intravenous insulin and glucose infusion is more physiologically rational and allows tighter glycemic control.[18] Proposed regimens include either separate insulin and glucose infusions or a single infusion of glucose, insulin, and potassium.

Studies comparing intravenous insulin infusion to subcutaneously delivered insulin generally found that tighter glycemic control was achieved using the intravenous route.[19–21] Drawing conclusions from those studies is difficult, however, because of methodological problems. In one study, patients randomized to intravenous insulin had lower glucose levels on admission.[19] Another study failed to describe the subjects' baseline characteristics and found significantly improved glycemic control at only two of six time points over 72 hours.[20] Rates of hypoglycemia are often not reported, but in one study, three of six patients managed with intravenous insulin required extra doses of glucose to prevent hypoglycemia.[21]

Currently, there is insufficient evidence to advocate tight perioperative glucose control. A reasonable goal would be to keep blood glucose under 250 mg/dl. More stringent control should be attempted only when the risk of hypoglycemia is deemed low. Likewise, no compelling data support one regimen of perioperative insulin delivery over the other. Physicians should choose the method of insulin delivery based on patient-specific criteria as well as the experience and familiarity of their local hospital staff in implementing the different regimens.

Reducing Postoperative Cardiac Complications With β-Blockers

Cardiac complications, particularly postoperative myocardial infarction, represent a major source of perioperative morbidity and mortality. Much of the literature on perioperative medicine focuses on approaches to assessing cardiac risk in patients undergoing noncardiac surgery. Less information is available on ways to prevent cardiac complications. One promising strategy is to place high-risk surgical patients on β-adrenergic blocking drugs. Surgical stress increases sympathetic tone and causes tachycardia and hypertension. It is hypothesized that this ultimately leads to ischemia and infarction. If that is true, then sympathetic blockade with β-blockers could prevent cardiac complications.

Several studies have examined the effects of β-blockers on myocardial ischemia during surgery. β-Blockers decreased frequency and duration of intraoperative ischemia as detected by single-lead ECG monitoring.[22,23] The studies, however, suffered from lack of blinding and inadequate randomization. Furthermore, intraoperative ischemia is a soft end-point that cannot be used as a surrogate for clinically important end-points such as myocardial infarction and cardiac death. Two nonrandomized studies found that perioperative β-blockers reduced the incidence of postoperative myocardial infarction in vascular surgery patients. Study design limited the strength of the conclusion, however. One study (retrospective cohort design) used a historical cohort as the control group.[24] In the other study (case-control design), it was unclear whether cases and controls had equal risk factor profiles for developing cardiac complications.[25]

A randomized, double-blinded, placebo-controlled trial of perioperative atenolol strengthens the evidence that β-blockers prevent perioperative cardiac complications.[26] Two hundred patients received either intravenous and oral atenolol or placebo while admitted for noncardiac surgery. All patients had known coronary artery

disease or had at least two risk factors for atherosclerosis. Treatment, which was well tolerated, began immediately before surgery and continued until discharge or for up to 1 week after surgery. Mortality and incidence of myocardial infarction did not differ at time of discharge. After 2 years of follow-up, however, the mortality was 55% lower in the atenolol-treated patients. Event-free survival (survival free from myocardial infarction, unstable angina, congestive heart failure requiring therapy, or need for revascularization) also improved. Based on these results, the authors of the American College of Physicians' guidelines for preoperative cardiac evaluation recommend perioperative β-blockers for patients with known, or at high risk for, coronary artery disease.[27]

The trial of perioperative atenolol is methodologically sound, but randomization results raise some questions about the findings. More patients in the atenolol arm had been on β-blockers before enrollment, possibly suggesting better outpatient care. It is not noted whether there were differences in usage of other drugs known to reduce cardiovascular morbidity and mortality, such as aspirin and HMG Co-A reductase inhibitors. Furthermore, it appears that the control arm consisted of sicker patients. While not reaching statistical significance, more patients receiving placebo had known coronary disease, prior myocardial infarction, typical angina, diabetes, and prior revascularization. A final concern is the delay of weeks to months observed between surgery and the development of complications. The authors hypothesize that sympathetically mediated perioperative ischemia predisposes patients to later myocardial infarction and that β-blockers prevented complications by ameliorating this harmful sympathetic tone. The study did not have adequate power to detect a difference in in-hospital morbidity and mortality.

Despite these limitations, the results of the study are compelling. No other intervention has been shown to reduce postoperative cardiovascular mortality in a randomized trial. The study included patients with both known and suspected coronary artery disease. Clearly, patients with known coronary artery disease should receive β-blockers in the absence of significant contraindications, regardless of whether surgery is anticipated. β-Blockers should also be considered a first-line drug for presurgical patients with uncontrolled hypertension. For patients who merely have risk factors for coronary artery disease, it is unclear whether β-blockers should be started "just to get the patient through surgery."

REFERENCES

1. Durack DT. Prevention of infective endocarditis. N Engl J Med 1995; 332:38–44

2. Dajani AS, Taubert KA, Wilson W, et al. Prevention of bacterial endocarditis: recommendations by the American Heart Association. JAMA 1997; 277:1794–1801

3. van der Meer JT, Thompson J, Valkenburg HA, Michel MF. Epidemiology of bacterial endocarditis in The Netherlands. II. Antecedent procedures and use of prophylaxis. Arch Intern Med 1992; 152:1869–1873

4. Horstkotte D, Rosin H, Friedrichs W, Loogen F. Contribution for choosing the optimal prophylaxis of bacterial endocarditis. Eur Heart J 1987; 8(supp J): 379–381

5. Imperiale TF, Horwitz RI. Does prophylaxis prevent postdental infective endocarditis? A controlled evaluation of protective efficacy. Am J Med 1990; 88:131–136

6. van der Meer JT, van Wijk W, Thompson J, Vandenbroucke JP, Valkenburg HA, Michel MF. Efficacy of antibiotic prophylaxis for prevention of native-valve endocarditis. Lancet 1992; 339:135–139

7. Clemens JD, Ransohoff DF. A quantitative assessment of pre-dental antibiotic prophylaxis for patients with mitral-valve prolapse. J Chron Dis 1984; 37:531–544

8. Cannegieter SC, Rosendaal FR, Briet E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. Circulation 1994; 89:635–641

9. Kearon C, Hirsh J. Management of anticoagulation before and after elective surgery. N Engl J Med 1997; 336:1506–1511

10. Eckman MH, Beshansky JR, Durand-Zaleski I, Levine HJ, Pauker SG. Anticoagulation for noncardiac procedures in patients with prosthetic valves. Does low risk mean high cost? JAMA 1990; 263:1513–1521

11. Katholi RE, Nolan SP, McGuire LB. Living with prosthetic heart valves: subsequent noncardiac operations and the risk of thromboembolism or hemorrhage. Am Heart J 1976; 92:162–167

12. Katholi RE, Nolan SP, McGuire LB. The management of anticoagulation during noncardiac operations in patients with prosthetic heart valves: a prospective study. Am Heart J 1978; 96:163–165

13. Tinker JH, Tarhan S. Discontinuing anticoagulant therapy in surgical patients with cardiac valve prostheses: observations in 180 operations. JAMA 1978; 239:738–739

14. Stagnaro-Green A. Perioperative glucose control: does it really matter? Mt Sinai J Med 1991; 58:299–304

15. McMurray JF. Wound healing with diabetes mellitus. Better glucose control for better wound healing in diabetics. Surg Clin North Am 1984; 64:769–778

16. Gottrup F, Anderson TT. Healing of incisional wounds in stomach and duodenum: the influence of experimental diabetes. J Surg Res 1981; 31:61–68

17. Zerr KJ, Furnary AP, Grunkemeier GL, Bookin S, Kanhere V, Starr A. Glucose control lowers the risk of wound infection in diabetics after open heart operations. Ann Thorac Surg 1997; 63:356–361

18. Hirsch IB, Paauw DS. Inpatient management of adults with diabetes. Diabetes Care 1995; 18:870–878

19. Christiansen CL, Schurizek BA, Malling B, Knudsen L, Alberti KGMM, Hermansen K. Insulin treatment of the insulin-dependent diabetic patient undergoing minor surgery: continuous intravenous infusion compared with subcutaneous administration. Anaesthesia 1988; 43:533–537

20. Thomas DJB, Platt HS, Alberti KGMM. Insulin-dependent diabetes during the peri-operative period: an assessment of continuous glucose-insulin-potassium infusion, and traditional treatment. Anaesthesia 1984; 39:629–637

21. Taitelman U, Reece EA, Bessman AN. Insulin in the management of the diabetic surgical patient: continuous intravenous infusion vs subcutaneous administration. JAMA 1977; 237:658–660

22. Pasternack PF, Grossi EA, Baumann FG, et al. Beta blockade to decrease silent myocardial ischemia during peripheral vascular surgery. Am J Surg 1989; 158:113–116

23. Stone JG, Foex P, Sear JW, Johnson LL, Khambatta HJ, Triner L. Myocardial ischemia in untreated hypertensive patients: effect of a single small oral dose of a beta-adrenergic blocking agent. Anesthesiology 1988; 68:495–500

24. Pasternack PF, Imparto AM, Baumann FG, et al. The hemodynamics of β-blockade in patients undergoing abdominal aortic aneurysm repair. Circulation 1987; 76(supp III):III-1–III-7

25. Yeager RA, Moneta GL, Edwards JM, Taylor LM, McConnell DB, Porter JM. Reducing perioperative myocardial infarction following vascular surgery. Arch Surg 1995; 130:869–873

26. Mangano DT, Layug EL, Wallace A, Tateo I. Effects of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. N Engl J Med 1996; 335:1713–1720

27. American College of Physicians. Guidelines for assessing and managing the perioperative risk from coronary artery disease associated with major noncardiac surgery. Ann Intern Med 1997; 127:309–312

Articles

A Randomized Double-Blind Study of the Effect of Distant Healing in a Population With Advanced AIDS

Report of a Small Scale Study

FRED SICHER, MA; ELISABETH TARG, MD; DAN MOORE II, PhD; *and* HELENE S. SMITH, PhD; *San Francisco, California*

A recent editorial called for "the scientific community to stop giving alternative medicine a free ride" (Angell M, Kassirer JP. Alternative medicine: the risks of untested and unregulated remedies. N Engl J Med 1998; 339:841). We agree. Now is the time for scientists to be courageous, as well as careful and precise, to help separate truth from hope and fact from myth. The paper published below is meant to advance science and debate. It has been reviewed, revised, and re-reviewed by nationally known experts in biostatistics and in complementary medicine. It reports a 6-month blinded study of 40 patients with AIDS who knew they might receive distant healing treatments representing a variety of traditions. Patients who received treatment had a statistically significant more benign course than control subjects. Does the paper prove that prayer works? No. The authors call for more research, as do we and the reviewers, for a number of reasons. We note that the study was relatively short and analysed rather few patients. No treatment-related mechanisms for the effects were posited. The statistical methods can be criticized. We have chosen to publish this provocative paper to stimulate other studies of distant healing and other complementary practices and agents. It is time for more light, less dark, less heat.

—Linda Hawes Clever, MD
Editor

Various forms of distant healing (DH), including prayer and "psychic healing," are widely practiced, but insufficient formal research has been done to indicate whether such efforts actually affect health. We report on a double-blind randomized trial of DH in 40 patients with advanced AIDS. Subjects were pair-matched for age, CD4+ count, and number of AIDS-defining illnesses and randomly selected to either 10 weeks of DH treatment or a control group. DH treatment was performed by self-identified healers representing many different healing and spiritual traditions. Healers were located throughout the United States during the study, and subjects and healers never met. Subjects were assessed by psychometric testing and blood draw at enrollment and followed for 6 months. At 6 months, a blind medical chart review found that treatment subjects acquired significantly fewer new AIDS-defining illnesses (0.1 versus 0.6 per patient, $P = 0.04$), had lower illness severity (severity score 0.8 versus 2.65, $P = 0.03$), and required significantly fewer doctor visits (9.2 versus 13.0, $P = 0.01$), fewer hospitalizations (0.15 versus 0.6, $P = 0.04$), and fewer days of hospitalization (0.5 versus 3.4, $P = 0.04$). Treated subjects also showed significantly improved mood compared with controls (Profile of Mood States score –26 versus 14, $P = 0.02$). There were no significant differences in CD4+ counts. These data support the possibility of a DH effect in AIDS and suggest the value of further research.

(Sicher F, Targ E, Moore D, Smith HS. A randomized double-blind study of the effect of distant healing in a population with advanced AIDS—report of a small scale study. West J Med 1998; 169:356–363)

Distant healing (DH) is defined as a conscious, dedicated act of mentation attempting to benefit another person's physical or emotional well-being at a distance. Various forms of DH, including prayer and some forms of spiritual healing, are widely reported and subscribed to in the United States.[1,2] Anecdotal experience with DH has

From the Geraldine Brush Cancer Research Institute (Mr Sicher and Drs Targ, Moore, and Smith), California Pacific Medical Center; Sausalito Consciousness Research Laboratory (Mr Sicher); and Departments of Psychiatry (Dr Targ), Statistics (Dr Moore), and Medicine (Dr Smith), University of California, San Francisco, California.

Reprint requests to Elisabeth Targ, MD, California Pacific Medical Center, 2300 California St, Suite 204, San Francisco, CA 94115. E-mail: etarg@cooper.cpmc.org

This work was supported in part by grants from the Sausolito Consciousness Research Laboratory, the Institute of Noetic Sciences, and the Parapsychology Foundation.

ABBREVIATIONS USED IN TEXT

ADD = AIDS-defining disease
BHS = Boston Health Study
DH = distant healing
MOS = Medical Outcomes Survey for HIV
POMS = Profile of Mood States
WPSI = Wahler Physical Symptom Inventory

stimulated a substantial body of research including at least 131 laboratory-published studies reviewed by Benor,[3] of which 56 found significant effects. Many of the studies, however, lacked rigorous control, measured only responses *in vitro*, involved only brief periods of influence, or did not include extended follow-up. The medical literature does contain a report of a rigorously controlled clinical study by Byrd,[4] who investigated the effects of intercessory prayer for 383 patients sequentially admitted to the San Francisco General Hospital Coronary Care unit. The study reported a significant improvement in hospital course and decreased medical complications in the treated group, but the period of medical follow-up was limited to the time each subject spent in the hospital, so delayed effects were not studied. In addition, outcome measures were not predefined. Thus, the longer-term efficacy of DH remains unstudied, and additional, scientifically rigorous studies are required to establish whether DH can be an effective intervention for life-threatening disease.

For these reasons, and without having conducted any previous DH studies at all, we chose to evaluate DH in a population of advanced AIDS patients with 6-month follow-up. Our initial study was a double-blind pilot study of 10 treated and 10 control subjects conducted during July 1995 through January 1996. The pilot study suggested both medical and psychological benefits of distant healing. Four of the 10 control group subjects died, with no deaths occurring in the treatment group, but the result was confounded by age (those who died were older). As a result, in the second larger study (reported here in full) a pair-matched design was used to control for factors shown to be associated with poorer prognosis in AIDS,[5] specifically age, T cell count, and illness history. Additionally, an important intervening medical factor changed the endpoint in the study design. The pilot study was conducted before the introduction of "triple-drug therapy" (simultaneous use of a protease inhibitor and at least two antiretroviral drugs), which has been shown to have a significant effect on mortality.[6] For the replication study (July 1996 through January 1997, shortly after widespread introduction of triple-drug therapy in San Francisco), differences in mortality were not expected and different endpoints were used in the study design. Based on results from the pilot study, we hypothesized that the DH treatment would be associated with *1*) improved disease progression (fewer and less severe AIDS-defining diseases [ADDs] and improved $CD4^+$ level), *2*) decreased medical utilization, and *3*) improved psychological well-being. The results of this replication study are reported below.

Subjects and Methods

Forty subjects were recruited by distributing fliers at clinics and at AIDS-related events and through advertisements in both gay and mainstream newspapers in the San Francisco Bay Area. Efforts were made to reach a wide range of socio-demographic populations. All subjects were required to meet the criteria of the Centers for Disease Control AIDS category C-3 ($CD4^+$ cell count <200 cells/µl, history of at least one ADD)[7] and to be taking *Pneumocystis carinii* pneumonia prophylaxis. Subjects signed informed consent, were photographed, and were randomly assigned on a double-blind basis to either DH or a control group. Subjects were told they had a 50-50 chance of receiving the DH treatment. Both groups continued to receive standard medical care at their primary care sites. Subjects were pair-matched by age, $CD4^+$ count, and number of ADDs before randomization.

Data acquisition

Subjects came to the laboratory or were visited at home to complete baseline and repeated measures at enrollment, at the end of the 10-week treatment intervention, and at follow-up 12–14 weeks later (Fig. 1). Measurements taken were $CD4^+$ count, psychological distress as measured by the Profile of Mood States (POMS),[8] physical symptoms as measured by the Wahler Physical Symptom Inventory (WPSI),[9] and quality of life as measured by the Medical Outcomes Survey (MOS) for HIV.[10] In addition, subjects reported doctor visits, hospitalizations, illness recovery, and onset of new illnesses. To verify the report, 6 months from the start of the study a blind medical chart review was performed by a study physician who catalogued outpatient doctor visits, hospitalizations, and remission or development of ADDs over the study interval. The review was done at 6 months only because of the focus of the study on extended treatment effects. Additional variables included subject's belief in the efficacy of DH, years HIV-positive, previous ADDs, protease inhibitor use, triple-drug therapy use, site of medical care delivery, use of complementary health practices, social support for study participation, drug and alcohol use, and demographics. Subjects were also asked, in a self-administered questionnaire, which group they thought they were in, treatment or control. For the one subject who died near the end of the study, all data were collected except the final $CD4^+$ count.

Evaluation of illness severity

To control for the variation in severity and prognosis of different AIDS-related illnesses, all illnesses were scored according to the Boston Health Study (BHS) Opportunistic Disease Score,[11] which includes both AIDS-defining and secondary AIDS-related diseases. The BHS severity scoring system has been validated in predicting survival in two large populations of AIDS patients. New ADDs were counted as "ADDs acquired" only if blind chart review revealed no prior diagnosis of the condition; the only exception to this rule was Kaposi's sarcoma. Because cutaneous Kaposi's sarcoma

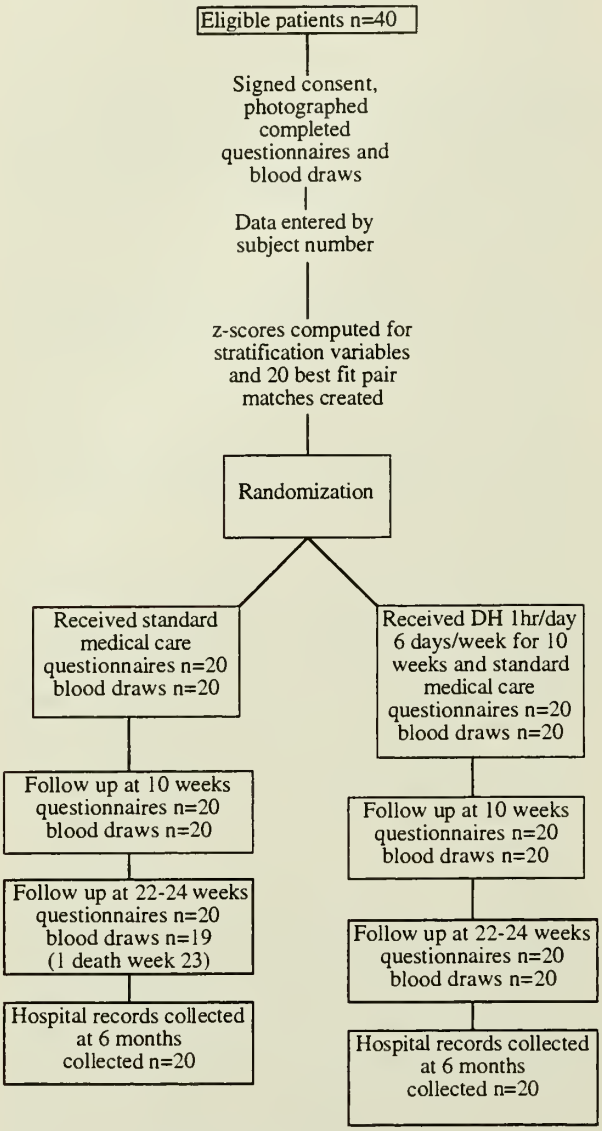


Figure 1.—Study flow chart.

is scored in a different severity category than visceral Kaposi's sarcoma, patients progressing from cutaneous to visceral Kaposi's sarcoma were counted as having acquired a new illness. Relapsing and remitting opportunistic diseases such as thrush or herpes or non–AIDS-defining bacterial infections were counted only once, whether or not there were recurrences. Recoveries from ADDs were tabulated when subjects' medical charts specifically stated a recovery had occurred or that there had been no evidence of the illness for at least 3 months.

Pair matching

Pair matching was done to control as much as possible for variation in outcomes that might be related to major disease progression and survival predictors, as indicated by the pilot study and in the medical literature.[6,11] The variables were age, baseline $CD4^+$ (T cell) count, and history of ADDs (sum of previous and current ADDs). These three variables were used to form matched subject pairs. First, a normalized z score was computed for each subject for each variable by subtracting the mean for all subjects and dividing the result by the standard deviation for all subjects. Next, all pairwise sums-of-squared differences in z scores between subjects (over the three variables) were computed. For each subject, an average difference from all the other subjects was calculated. Starting with the subject with the largest average difference, the closest match was found. The two matched subjects were eliminated from the list and the procedure was iterated until all 40 subjects were paired. A computer-generated binary random number was then used to randomly assign one member of each pair to treatment and one to control.

Blinding procedures

All subject enrollment interviews were performed by one of two staff members who assigned subjects enrollment numbers. After enrollment was complete, a third staff member used a random number table to assign "study code" numbers to each of the enrollment numbers; these were substituted in the computer and used in randomization. Medical charts were obtained at the end of the study; names were removed from all text, and charts were assigned a new set of code numbers before they were reviewed. The chart reviewer did not know which subjects were in which group at the time of review. All data were entered into the computer by a research assistant who was blind to group assignment. Subjects learned their group assignment 1 year after the the study ended.

Treatment procedures

At the time of enrollment all subjects were photographed, and subject information packets including 5×7-inch color photograph, first name, $CD4^+$ count, and current symptoms were prepared by a research assistant. Ten copies of each packet were made and marked with removable labels indicating the subject's enrollment number. After randomization, the enrollment numbers were removed from the packets and replaced with the study codes. The packets were then divided into treatment and control groups based on the randomization results. Control subject packets were retained unopened in a locked file drawer. Treatment subject packets were grouped in batches of five to be sent to each healer. Each of the five envelopes sent to the healers was marked with the day to be opened to begin the healing period for that patient.

Healers

Forty DH practitioners, including 12 from the pilot study, were recruited via professional healing associations and schools of healing. Eligibility criteria were minimum 5 years regular ongoing healing practice, previous healing experience *at a distance* with at least 10 patients, and previous healing experience with AIDS.

Healers had an average of 17 years of experience and had previously treated an average of 106 patients at a distance. Practitioners included healers from Christian, Jewish, Buddhist, Native American, and shamanic traditions as well as graduates of secular schools of bioenergetic and meditative healing. Practitioners were not paid and understood that the study could not evaluate the abilities of any individual practitioner. Healers were residing at various locations throughout the United States. The site from which they performed their healing was not restricted.

Healing treatment

A rotating healing schedule randomized healers to subjects on a weekly basis to minimize possible differences in healer effectiveness. Thus, each subject in the DH group was treated by a total of 10 different practitioners, while each practitioner worked every other week treating a total of 5 subjects. Each healer received five consecutively numbered subject information packets with instructions specifying the day to begin treatment on each subject. Healers were asked to work on the assigned subject for approximately 1 hour per day for 6 consecutive days with the instruction to "direct an intention for health and well-being" to the subject. Healers completed logs for each healing session, indicating period of healing, specific technique, and any impressions of the subject's illness. Subjects never met practitioners and did not know whether they were in the DH group, where the practitioners were located, nor at what time the DH might occur. Before the intervention, study personnel encouraged and motivated healers via letters and phone calls stressing the importance of the study and their individual efforts.

Statistical methods

Baseline and outcome comparisons between the two groups involved three statistical tests: paired *t* test for all continuous or multilevel variables, Wilcoxon signed-rank test when the data appeared to be skewed or contained outliers, and McNemar's test for 2×2 tables comparing paired binary variables. For study outcomes where $P < 0.05$, since many of the outcomes had skewed or clumped distributions (caused by tied values in outcome), a randomization test[12] was also used to obtain an "exact" *P* value for the observed outcome.

In addition, because study outcomes may be correlated, Hotelling's T-square statistic was used to determine whether there was a treatment effect on the array of 11 medical and psychological outcomes. Again, since this statistic assumes multivariate normality of the outcomes (which is not the case), statistical significance of the outcome array was further assessed by conducting a randomization test on the T-square statistic. A randomization test is based on comparing a set of observed outcomes with those generated by randomly permuting the treatment-control assignment of subjects. Randomization tests are distribution free, that is, no assumption concerning the distribution of the test statistic is required. In this way, an unbiased determination of significance is obtained without assumptions concerning the distribution of the test statistic. (An informative discussion of randomization tests in a medical setting is contained in a recent issue of *The American Statistician*.[13]) This method for determining statistical significance was necessitated by the nature of the outcomes data.

We also examined the effects of differences in baseline factors (those with two-sided $P < 0.2$) on outcome variables by stratifying on levels of baseline factor when they were discrete and by analysis of covariance when they were continuous.

Results

Baseline comparisons

Subjects were 37 men and 3 women with a mean age of 43 (Table 1). Only one patient (DH group) had a history of intravenous drug use. There were no statistically significant differences on any baseline measures between the treated and control groups, including those used for pair-matching, or in ongoing AIDS management-related variables, such as use of triple-drug therapy (Table 1). There were several near-significant differences ($P < 0.20$), however. All five baseline smokers and all four minorities were in the control group ($P = 0.06$ and $P = 0.12$, respectively). Of note, two treated subjects resumed their smoking habit during the study period (one near the beginning and one near the middle), reducing group smoking differences. The control group also was HIV-positive for a shorter time (7.3 versus 9.0 years, $P = 0.11$), showed a trend toward lower initial psychological distress scores (POMS 43 versus 62, $P = 0.19$), and had used fewer alternative therapies (2.7 versus 4.2, $P = 0.10$).

A review of primary care sites found no significant differences in site or type of medical practice (university, specialty clinic, solo practice). Review of charts, each containing complete medical history, found no major comorbid conditions (heart disease, cancer, diabetes) in either group. A majority of subjects (85%) expressed an *a priori* belief in the benefit of DH. The level of belief at baseline was nearly equal for both groups, and the belief showed no correlation with medical outcomes.

Medical and psychosocial outcomes

Over the 6-month study period, the DH group experienced significantly fewer outpatient doctor visits, fewer hospitalizations, fewer days of hospitalization, fewer new ADDs, and a significantly lower illness severity level as defined by the BHS scale (Table 2). All diseases acquired are listed in Table 3. At 6 months, the DH group also showed significantly improved mood compared with controls as measured by the POMS, reflecting improvement on four of six subscales (depression, $P < 0.02$; tension, $P < 0.02$; confusion; $P < 0.002$; fatigue, $P < 0.02$). Differences on the WPSI and MOS were not significant between groups. One death occurred in the control group, after the patient's follow-up questionnaire had

TABLE 1.—*Baseline and AIDS Management-Related Variables*

n	*Treated* 20	*Control* 20	*Two-sided P*[1]
Age (years)	42.9 ± 7.2	43.2 ± 6.4	0.80
Sex (% female subjs.)	10	5	1.00
Ethnic minority (% subjs.)	0	20	0.12
Education[2]	4.1 ± 0.6	3.9 ± 1.0	0.38
Baseline AIDS-related factors			
Years HIV positive	9.0 ± 3.5.	7.3 ± 3.1	0.11
CD4 cell number/ml	90.3 ± 66.0	83.8 ± 70.9	0.55
No. existing ADDs	1.4 ± 1.3	1.3 ± 1.4	0.65
No. prior ADDs	1.9 ± 1.3	2.1 ± 1.4	0.58
ADD severity[3]	5.4 ± 3.0	5.0 ± 3.3	0.49
Interventions during study			
Triple-drug therapy[4]			
Throughout study	70	80	0.72
At least 2 months	20	15	1.00
Protease inhibitors	90	95	1.00
Pneumonia carinii prophylaxis	100	100	1.00
No. alternative therapies[5]	4.2 ± 2.6	2.7 ± 2.0	0.10
Support[6]	85	95	0.61
Psychotherapy	45	50	1.00
Baseline subjective measures			
WPSI score	1.64 ± 0.72	1.69 ± 0.80	0.86
POMS score	62.3 ± 46.7	42.8 ± 39.9	0.16
MOS score[7]	−0.01 ± 0.8	−0.01 ± 0.8	1.00
Baseline personal habits			
Smokers	0	25	0.06
Recreational drug use[8]	20	20	1.00
Alcohol use[9]	0.4 ± 0.6	0.8 ± 1.1	0.27
Exercise[10]	1.4 ± 1.3	1.9 ± 1.4	0.34
Meditation practice	60	75	0.50
Religious/spiritual practice	90	80	0.66
Belief in DH[11]	2.8 ± 0.6	2.9 ± 0.4	0.33

Data are means ± SD or %.

[1]Paired *t* test for continuous variables, Wilcoxon signed-Rank test for variables with outliers, McNemar's test for binary variables; all tests are of matched paired differences. "Matched" refers to variables used for pair matching.

[2]Some high school = 1, high school graduate = 2, some college = 3, college graduate = 4, graduate degree = 5.

[3]Boston Health Study opportunistic disease score.

[4]Simultaneous use of a protease inhibitor and at least two antiretroviral drugs.

[5]Acupuncture, psychic healing or prayer, Chinese herbs, yoga, biofeedback, guided imagery, Chi Gong, nutritional supplements or vitamins, special diet, group therapy, or other.

[6]Number of subjects reporting study participation support from family or community members.

[7]Normalized mean score for 10 factors.

[8]Four subjects in each group used crack cocaine or oral amphetamines; one treatment subject also used IV amphetamines.

[9]No alcohol = 0, once or twice a week = 1, several times a week = 2, heavily on weekends = 3, daily = 4.

[10]No exercise = 0, once a week = 1, two or three times a week = 2, four or five times a week = 3, daily = 4.

[11]"I doubt it" = 0, "Maybe" = 1, "Probably" = 2, "Yes, definitely" = 3.

been completed but 1 week before the 6-month study endpoint. There was a nonsignificant trend toward increase in $CD4^+$ count for both groups, although the two groups did not differ significantly on this measure. Thus, the DH treatment was associated with significantly better outcomes on 6 of the 11 medical outcome measures.

At study midpoint, immediately after the treatment intervention, subjects were asked if they thought they had been in the DH or control group. Two subjects (one from each group) did not respond. Nine of the DH group subjects and 13 of the control group subjects believed they were in the DH group ($P = 0.32$; Fisher's exact test). Additional analysis was done to investigate possible correlation between subject belief about group assignment and study outcomes. Belief about group assignment did not correlate with any study outcome except $CD4^+$ change ($P = 0.05$). This correlation no longer held when subjects were again asked to guess group assignment at the end of the 6-month study period ($P = 0.28$). At the end of the study period, subjects who had experienced more recoveries did tend to correctly guess they had been in the treatment group ($P = 0.05$).

TABLE 2.—*Medical Course Over 6-Month Study*

Medical Outcome	*Treated (n = 20)*	*Control (n =20)*	*Two-tailed P*[1]
Outpatient visits	185 (9.2 ± 5.9)	260 (13.0 ± 7.0)	0.01
Hospitalizations	3 (0.15 ± 0.5)	12 (0.6 ± 1.0)	0.04
Days of hospitalization	10 (0.5 ± 1.7)	68 (3.4 ± 6.2)	0.04
Illness severity[2]	16 (0.80 ± 1.15)	43 (2.65 ± 2.41)	0.03
ADDs acquired	2 (0.1 ± 0.3)	12 (0.6 ± 0.9)	0.04
ADD recoveries	6 (0.3 ± 0.6)	2 (0.1 ± 0.3)	0.23
$CD4^+$ change (/μl)[3]	31.1 ± 54.9	55.5 ± 102.0	0.55
Deaths	0	1	1.00
Change in POMS score (distress)	−25.7 ± 46.0	14.2 ± 49.0	0.02
Change in MOS	0.2 ± 0.8	−0.2 ± 0.8	0.15
Change in WPSI	−0.2 ± 0.6	0.1 ± 0.9	0.31

Data are *n* (means ± SD) or means ± SD.

[1]Wilcoxon signed-rank test for the first seven outcomes; paired *t* tests for the last three outcomes; McNemar's test for number of deaths. Due to clumpiness of the data for variables near $P = 0.05$, the randomization test was also performed with the following results: hospitalizations, $P = 0.06$; days of hospitalization, $P = 0.04$; ADD severity score, $P = 0.03$; ADDs acquired, $P = 0.06$.

[2]Boston Health Survey opportunistic disease severity score, includes ADD and AIDS-related illness (Table 3).

[3]*n* =19 in the control group (one subject died).

Baseline effects on outcomes

Where baseline group differences were near-significant ($P < 0.20$), these variables were examined for correlation with all study outcomes. We found no effects of the baseline differences in smoking, number of years HIV-positive, or number of alternative therapies used on any outcomes. As described above, the treatment group tended to have higher baseline POMS scores (more distress) than controls. Higher baseline psychological distress, in both groups, was significantly correlated with greater reduction in psychological distress at the end of the study ($P < 0.001$). When baseline POMS was used as a covariate to adjust the POMS change scores, the difference in POMS change scores switched from statistical significance in favor of the treated to significance in favor of the controls. Baseline POMS values did not significantly correlate with any of the medical outcomes, although, as expected, they did correlate with the other psychological measures.

Minority status (with all 4 minorities in the control group) showed a near-significant difference at baseline. When this variable was examined *within* the control group (4 minorities versus 16 nonminorities), no significant correlation with study outcomes was found. However, a stratified analysis on all subjects, which takes minority differences in treatment-control pairs into account, resulted in a change in the *P* values from 0.04 to 0.09 for number of hospital stays and from 0.04 to 0.08 for number of hospital days. The difference in minority status among treated and control did not significantly correlate with any other outcome variable.

Analysis of Outcome Array

Many of the outcomes in Table 2 are correlated with each other. Thus, it is useful to evaluate the treatment effect by using a statistic that takes into account these correlations. The results of the randomization test applied to Hotelling's T-square statistic indicated that the array of all outcomes is statistically significant ($P = 0.0154$; that is, in the 10,000 random samplings only 154 T-squares exceeded the observed Hotelling T-square statistic).

Discussion

The findings of decreased medical utilization, fewer and less severe new illnesses, and improved mood for the treated group compared with the controls supports a positive therapeutic effect of DH. This outcome is difficult to explain, particularly in this double-blind study where subjects, physicians, and study personnel did not know who was in the treatment group. There are two explanations other than a DH effect that, in principle, could explain these data.

First, differences between the group outcomes might be attributed to baseline medical or treatment differences. This possibility was not supported by univariate comparison of baseline AIDS-related variables, as shown in Table 1, where there were no statistically significant differences between the groups. Detailed analysis of baseline variables differing at $P < 0.20$ did find that higher baseline POMS scores were associated with greater improvement in POMS scores over the course of the study. By chance, patients in the treatment group showed more psychological distress at baseline, so their improved mood over the study interval may represent simply an effect of increased hope or expectation due to their participation in an intervention research study. The additional finding that adjusting for differences in baseline POMS caused a change in the direction of the beneficial effect is difficult to understand and is likely due to chance.

While baseline psychological state, as measured by the POMS, did correlate with psychological outcomes, it did not correlate with any of the medical outcomes. Detailed

TABLE 3.—*Distribution of AIDS-Related Illnesses Acquired During the Study*

n	*Treated* 20	*Control* 20
BHS severity group III (ADD)		
Kaposi's sarcoma (visceral)	0	1
Mycobacterium avium complex	1	1
BHS severity group II (ADD)		
Cytomegalovirus	0	2
HIV encephalitis	0	1
Coccidiomycosis	0	1
Wasting syndrome	0	1
Pneumocystis carinii pneumonia	1	1
BHS severity group I (ADD)		
Esophageal candidiasis	0	2
Kaposi's sarcoma (cutaneous)	0	1
Recurrent pneumonia	0	1
BHS severity group I (AIDS-related)		
Pseudomonas sepsis	0	1
Meningitis sepsis	0	1
Oral leukoplakia	0	1
Kaposi's sarcoma metastasis (cutaneous)	0	1
Renal insufficiency	0	2
Oral thrush	1	5
Herpes (genital/rectal)	1	3
Oral ulcers	1	0
Anemia	3	1
Bacterial infection	5	8
AIDS-related illnesses not scored by BHS		
Cervical dysplasia	1	2
Diarrhea	2	6
Peripheral neuropathy	5	6

Data are number of cases; presence or absence was based on blind medical chart review.

examination of the effects of differences in baseline factors on outcomes also found a marginal effect of difference in minority status for hospitalizations. This is an interesting finding but is weakened by the fact that in this study no minorities received DH. In fact, when hospitalizations and hospital days are examined within the control group alone, ethnicity does not make a significant difference. Because our sample of minorities was so small and they all ended up in the control group, the fact that they had proportionately more hospitalizations is very hard to interpret. Adjustment for their contributions has only a small effect on the P value, but clearly a larger sample with more minorities would be required to determine whether DH was affecting hospitalizations. It is important to point out that having conducted 50 statistical tests to find interactions between differences in baseline factors and outcomes (excluding death), only two were found, which is the number expected by chance. We found no baseline differences with $P < 0.20$, which could explain differences in number of doctor visits or number or severity of new ADDs. Although there was a near-significant trend for more smokers in the control group, by the study midpoint treatment subjects who resumed smoking brought the distribution into better balance. There was no correlation with smoking status and any study outcome. It does remain possible, however, that combinations of baseline variables or differences in some unmeasured variable may have influenced outcomes.

A second possible explanation for the data is an expectation or placebo effect, as when patient improvement occurs due to a belief about the effectiveness of a treatment.[14,15] This is especially worth examining given the finding that baseline psychological status may have affected change in psychological well-being during this study. The expectation effect should lead to better outcomes among subjects who believe they were in the treatment group, regardless of their true group assignment. Differences in medical outcomes were related to true group assignment, however, and unrelated to assignment belief. The only outcome measure showing correlation with subject belief was $CD4^+$ count, and interestingly, this finding held up only at the study midpoint and not at the end of the study. Possibly, early in the study, subjects who believed they were in the treatment group came to this belief because they knew from some other source that their $CD4^+$ count was rising. We cannot eliminate the possibility that hope or expectation as reflected by the subject's guess may have affected $CD4^+$ count, but $CD4^+$ count did not differ between the two study groups, so it does not seem likely this factor affected the differential study outcomes.

The findings of reduction in medical utilization and development of fewer and less severe new illnesses suggest, as in the Byrd study, a global rather than a specific DH effect. This study made an initial attempt to identify a specific marker of DH action by including $CD4^+$ counts. Despite the differences in medical morbidity, however, there were no significant differences between the groups in $CD4^+$ counts, which generally remained very low. Recent evidence suggests that viral load may be a better outcome predictor than $CD4^+$ count.[16] Future studies should seek specific markers of DH effect with viral load and natural killer cell activity.

Existing medical understanding offers no mechanism to account for a finding of healing at a distance; however, science does not require a known mechanism to prove the existence of a phenomenon. As pointed out by Dossey,[17] for years no one knew how colchicine, morphine, aspirin, or quinine worked, yet they were known to be effective. Hand-washing, too, became standard medical practice well before a theory of infectious disease was described. Possible mechanisms for DH might include some form of mind-to-mind communication between patient and practitioner or some form of previously undescribed energy transfer. Such concepts are, of course, highly speculative and remain an area for future research.

The finding of reduced medical utilization and improved medical course in the DH group is both exciting and surprising, but it remains crucial for this work to be replicated to be more confident that the effect is real.

If the effect is robust, future studies will also need to compare different DH techniques and investigate the efficacy of DH in different illnesses and with different subject populations.

Acknowledgments

We thank G. Furst and R. Scott for their outstanding assistance with data management and collection and Drs. J. Kaiser, D. Karasic, and M. Cantwell for valuable discussions and suggestions. We especially thank all of the healers who donated their skills and time and made this project possible.

REFERENCES

1. Eisenberg DM, Kessler RC, Foster C, Norlock FE, Calkins DR, Delbanco TL. Unconventional medicine in the United States. Prevalence, costs, and patterns of use. N Engl J Med 1993; 328:246–252

2. Dossey L. Healing Words. New York, Harper Collins Publishers, 1993

3. Benor DJ. Healing Research. Deddington, UK, Helix Editions, 1992

4. Byrd RC. Positive therapeutic effects of intercessory prayer in a coronary care unit population. South Med J 1988; 81:826–829

5. Saah AJ, Hoover DR, He Y, Kingsley LA, Phair JP. Factors influencing survival after AIDS: report from the Multicenter AIDS Cohort Study (MACS). J Acquir Immune Defic Syndr 1994; 7:287–295

6. Hammer SM, Squires KE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus indinivar in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. N Engl J Med 1997; 337:725–733

7. Centers for Disease Control and Prevention. Centers for Disease Control category C-3 AIDS index illnesses. MMWR 1994; 41:RR-17

8. McNair DM, Lorr M, Droppleman LF. Profile of Mood States manual. San Diego, 1992

9. Wahler HJ. Wahler Physical Symptoms Inventory manual. Los Angeles, Western Psychological Services, 1983

10. Wu AW, Rubin HR, Mathews WC, et al. A health status questionnaire using 30 items from the Medical Outcome Study. Preliminary validation in persons with early HIV infection. Med Care 1991; 29:786–798

11. Seage GR, Gastonis C, Weissman JS, Haas JS, Cleary PD, Fowler FJ. The Boston AIDS Survival Score (BASS)—a mulitdimensional AIDS severity instrument. Am J Pub Health 1997; 87:567–573

12.. Manly BFJ. Randomization, Bootstrap and Monte Carlo Methods in Biology, 2nd edition. London, Chapman and Hall, 1997

13. Ludbrook J, Dudley H. Why permutation tests are superior to *t* and *F* tests in biomedical research. Am Statistician 1998; 52:127–132

14. Shapiro AK. Placebo effects in medicine, psychotherapy and psychoanalysis. In, Bergin A, Garfied S (Eds): Handbook of Psychotherapy and Behavior Change. New York, Wiley, 1971, pp 437–439

15. Brown WA. The placebo effect. Sci Am 1998; 278:90–95

16. Mellors JM, Riwaldo CR, Cupta P, White RM, Todd JA, Kingsley LA. Prognosis in HIV-1 predicted by the quantity of virus in plasma. Science 1996; 272:1167–1170

17. Dossey L. Running scared: how we hide from who we are. Altern Ther 1997; 3:8–15

Articles

Prevalence of Antimicrobial Drug–Resistant *Streptococcus pneumoniae* in Washington State

PAMELA A. FRICK, PharmD; DOUGLAS J. BLACK, PharmD; JEFFREY S. DUCHIN, MD; SAM DELIGANIS, MBA; WILLIAM M. MCKEE, MD; *and* THOMAS R. FRITSCHE, MD, PhD; *Seattle, Washington*

We conducted a survey to assess the prevalence and geographic distribution of antimicrobial drug resistance among invasive isolates of *Streptococcus pneumoniae* in Washington State. Sequential sterile-site pneumococcal isolates were submitted from 13 hospital laboratories between 1 October 1995 and 30 January 1997. We serotyped 275 isolates from adults and children and determined minimum inhibitory concentrations (MIC) for commonly used antimicrobial drugs. Data were abstracted from medical records to compare differences in outcome and risk factors for infection. Of the 275 isolates, 73 (26.5%) were nonsusceptible to one or more antimicrobial drugs. Penicillin-nonsusceptible pneumococci (PNSP, MIC ≥0.1 μg/ml) accounted for 42 (15.3%) of the 275 isolates including 4 (1.5%) resistant strains (MIC ≥2 μg/ml). The 42 PNSP included serogroups 6, 9, 14, 19, and 23, all of which are represented in the 23-valent pneumococcal vaccine. PNSP were also nonsusceptible to trimethoprim/sulfamethoxazole (92.9%), erythromycin (38.1%), imipenem (28.6%), and ceftriaxone (23.8%). Forty-seven (17.1%) of the 275 isolates were multiple drug–nonsusceptible pneumococci (MDNSP). A significantly greater number of patients ≤12 years of age were infected with MDNSP compared with those >12 years. Prior use of antimicrobial drugs and an immunosuppressive disorder were risk factors for infection with PNSP. In summary, pneumococci nonsusceptible to penicillin and other antimicrobial drugs are prevalent among adults with invasive pneumococcal disease in Washington State. A large proportion of PNSP are resistant to other commonly used antimicrobial drugs. Local antibiotic susceptibility data should be considered when designing empiric treatment regimens.

(Frick PA, Black DJ, Duchin JS, Deliganis S, McKee WM, Fritsche TR. Prevalence of antimicrobial drug–resistant *Streptococcus pneumoniae* in Washington State. West J Med 1998; 169:364–369)

Streptococcus pneumoniae is a leading cause of bacterial pneumonia, meningitis, acute otitis media, and sinusitis worldwide. An estimated 40,000 people in the United States die each year from pneumococcal infection.[1] In most instances, treatment for suspected pneumococcal infections is begun empirically. The emergence of penicillin-nonsusceptible pneumococci (PNSP), however, has complicated treatment decisions. Penicillin-nonsusceptible *S. pneumoniae* was first isolated in Papua, New Guinea, in 1967 and has since been reported with increasing frequency in the United States, Europe, Australia, and many other areas around the world.[2–12]

Previous surveillance studies have characterized the rate of penicillin nonsusceptibility for specific communities to be 6.6% to 53%.[3–7] Although PNSP is still not reportable in the majority of US states, recent recommendations suggest basing empiric treatment on local susceptibility patterns.[13] Since data on the rate of PNSP in the Pacific Northwest have not been collected recently, this study was designed to assess the proportion and geographic distribution of invasive antimicrobial drug–resistant pneumococci in Washington State and identify risk factors for infection with PNSP, differences in clinical outcomes, and documented rates of pneumococcal vaccine use among people with invasive pneumococcal disease.

Methods

All pneumococcal isolates from normally sterile body sites (blood, cerebrospinal fluid, pleural fluid,

From the Schools of Pharmacy (Drs Frick and Black) and Medicine (Drs Duchin and Fritsche), University of Washington; Northwest Pharmaceutical Research Network (Mr Deliganis); and PRO-West (Dr McKee), Seattle, Washington.

Reprint requests to Douglas J. Black, PharmD, Department of Pharmacy, H375U Health Sciences Building, Box 357630, University of Washington, Seattle, WA 98195-7630. E-mail: dblack@u.washington.edu

This article was developed as a part of a quality improvement project conducted under the Health Care Quality Improvement Program of the Health Care Financing Administration, Baltimore, Maryland. The conclusions and opinions expressed and the methods used are those of the authors and not necessarily policy of the Health Care Financing Administration. The authors assume all responsibility for accuracy and completeness.

ABBREVIATIONS USED IN TEXT

CDC = Centers for Disease Control
CI = confidence interval
CNS = central nervous system
MDNSP = multiple drug–nonsusceptible pneumococci
MIC = minimum inhibitory concentration
PNSP = penicillin-nonsusceptible pneumococci
PRP = penicillin-resistant pneumococci
RR = relative risk
TMP/SMX = trimethoprim/sulfamethoxazole

peritoneal fluid, and middle ear fluid) of patients at selected hospitals in Washington State during the period from 1 October 1995 through 30 January 1997 were included in the study. Patient age, sex, specimen source, and specimen collection date were recorded. Based on periodic audits of microbiology laboratory records, hospitals were excluded from participation for failure to submit all sterile-site isolates. Participating hospitals were selected based on membership in the Northwest Pharmaceutical Research Network, a nonprofit network of health care settings collaborating in pharmaceutical outcomes research, and willingness to submit isolates. An appropriate institutional review board from each hospital approved the project.

Isolates were forwarded to the clinical laboratories of the University of Washington Medical Center, subcultured to ensure viability, and stored at −70°C in a suspension of 50% trypticase-soy-yeast extract broth and 50% fetal calf serum. Frozen isolates were thawed and cultured onto sheep blood agar plates (Heart Infusion Agar; Remel, Lenexa, KS) and incubated overnight at 35°C with ~5%–10% CO_2. Colonies were tested with 10% desoxycholate solution (Difco Laboratories, Detroit, MI). Thin smears of bacteria were prepared from a 0.8% saline suspension, air-dried, and heat-fixed. The smears were tested with the OMNI (polyvalent) pneumococcal antiserum (Statens Seruminstitut, Copenhagen, Denmark) and also for reactivity with each of nine pooled antisera to determine serogroup. Isolates that were bile-positive and displayed a colonial morphology consistent with *S. pneumoniae* were included in the study. Because the first 249 isolates were positive when tested with the OMNI antisera, further use was discontinued.

Antimicrobial susceptibility testing was conducted using a microdilution procedure. Customized minimum inhibitory concentration (MIC) plates were prepared by PML Microbiologicals (Portland, OR). The following concentrations of antimicrobials were prepared: penicillin, 0.008–4.0 µg/ml; clindamycin, 0.008–1.0 µg/ml; trimethoprim/sulfamethoxazole (TMP/SMX), 0.008/0.148–4.0/76 µg/ml; cefprozil, 0.06–32.0 µg/ml; vancomycin, 0.008–1.0 µg/ml; erythromycin, 0.008–4.0 µg/ml; ceftriaxone, 0.008–4.0 µg/ml; rifampin, 0.004–4.0 µg/ml; chloramphenicol, 0.06–8.0 µg/ml; and imipenem 0.004–1.0 µg/ml. A suspension of cells equal to that of a 0.5 McFarland turbidity standard was prepared in saline. One milliliter of the suspension was added to 29 ml sterile water and used to inoculate the microdilution plates using a disposable inoculating device purchased from PML Microbiologicals. Plates were incubated overnight at 35°C in an atmosphere containing 5%–10% CO_2. Growth in microtiter plates was read visually using a mirrored plate reader. MIC was defined as the lowest concentration of antimicrobial drug that inhibited visible growth. A quality control strain of *S. pneumoniae*, ATCC 49619, was tested simultaneously with each batch of patient isolates.

MIC values were interpreted using 1997 National Committee for Clinical Laboratory Standards (NCCLS) breakpoints (all values in µg/ml)[14]:

	Intermediate	Resistant
Penicillin	0.12–1.0	≥2.0
Clindamycin	0.5	≥1.0
TMP/SMX	1.0/19 to 2.0/38	≥4/76
Erythromycin	0.5	≥1.0
Ceftriaxone	1.0	≥2.0
Rifampin	2.0	≥4.0
Chloramphenicol	—	≥8.0
Imipenem	0.25 to 0.5	≥1.0

Nonsusceptibility was defined as an MIC at the intermediate level or higher. Multiple drug–nonsusceptible pneumococci (MDNSP) were defined as nonsusceptible to two or more antimicrobial drugs.

Data regarding risk factors for infection such as underlying diseases, location before admission, antimicrobial drug use in the previous month, and age were abstracted from the medical record. Immunosuppressed status was defined as the presence of AIDS, history of organ transplantation or lymphoma, treatment with immunosuppressive therapy, or neutropenia. Clinical outcomes such as length of hospital stay, admission to an intensive care unit (ICU), ICU length of stay, presence of complications (acute renal failure, assisted ventilation, hypotension, acute liver failure, or cardiac arrest), and mortality were assessed. Documentation of the use of the 23-valent pneumococcal vaccine was recorded. Random reliability reviews were completed on charts from each hospital by alternative abstractors to reduce interabstractor variability in data collection. All data was entered into an Epi Info data set (version 6.03; Centers for Disease Control and Prevention [CDC], Atlanta, GA) and then exported into SAS System for Windows (version 6.11) for data analysis. Relative risks (RRs) and their 95% confidence intervals (CIs) and Wilcoxon two-sample tests with a type I error level of 0.05 were used where indicated.

Results

Antimicrobial drug susceptibility data

We received 449 pneumococcal isolates from 23 hospitals during the 16-month study period. Eight hospitals submitting a total of 41 isolates were excluded from the study for failure to submit all sterile-site pneumococcal isolates,

TABLE 1.—*Antimicrobial drug nonsusceptibility for six S. pneumoniae serogroups, including nonsusceptibility to at least one antimicrobial drug and MDNSP*

		Isolotes Nonsusceptible									Nonsusceptible to At Leost One Antimicrobiol Drug	MDNSP
Serotype	Isolotes	Penicillin (PNSP)	TMP/SMX	Erythromycin	Ceftrioxone	Imipenem	Clindomycin	Chloromphenicol	Rifompin	Voncomycin		
14	44 (16.0)	7 (15.9)	8 (18.2)	2 (4.5)	1 (2.3)	1 (2.3)	1 (2.3)	0	0	0	9 (20.5)	8 (18.2)
9	41 (14.9)	10 (24.4)	9 (22.0)	4 (9.8)	2 (4.9)	1 (2.4)	0	1 (2.4)	0	0	12 (29.3)	8 (19.5)
6	30 (10.9)	9 (30.0)	18 (60.0)	9 (30.0)	0	1 (3.3)	2 (6.7)	2 (6.7)	1 (3.3)	0	20 (66.7)	13 (43.3)
19	27 (9.8)	9 (33.3)	12 (44.4)	6 (22.2)	4 (14.8)	4 (14.8)	0	3 (11.1)	0	0	12 (44.4)	9 (33.3)
23	18 (6.5)	6 (33.3)	13 (72.2)	3 (16.7)	3 (16.7)	5 (27.8)	0	4 (22.2)	0	0	14 (77.8)	6 (33.3)
4	21 (7.6)	0	2 (9.5)	1 (4.8)	0	0	1 (4.8)	0	0	0	3 (14.3)	1 (4.8)
Other	94 (34.2)	1 (1.1)	2 (2.1)	3 (3.2)	0	0	1 (1.1)	0	0	0	5 (5.3)	2 (2.1)
Total	275	42 (15.3)	64 (23.3)	28 (10.2)	10 (3.6)	12 (4.4)	5 (1.8)	10 (3.6)	1 (0.4)	0	75 (27.3)	47 (17.1)

Data are *n* (%). Susceptibility is defined in Methods.

and 133 isolates were excluded because of nonviability, collection from a nonsterile body site, duplication, or unknown hospital source. Antimicrobial susceptibility testing and serotyping were thus performed on 275 sterile-site isolates of *S. pneumoniae* from 11 community- and 2 university-based hospitals. Five hospitals are located in Seattle, six in the greater Puget Sound region (one in Olympia, three in Tacoma, one in Puyallup, one in Everett), and one each in Yakima and Spokane.

Of the 275 isolates, 258 (93.8%) were from blood. Other sources and numbers of isolates included middle-ear fluid, 5 (1.8%); cerebrospinal fluid, 4 (1.5%); pleural fluid, 4 (1.5%); peritoneal fluid, 1 (0.4%); bone marrow, 1 (0.4%); mastoid, 1 (0.4%); and brain biopsy, 1 (0.4%). One hundred nineteen (43.3%) were from Seattle hospitals, 93 (33.8%) from the greater Puget Sound region, 40 (14.5%) from Yakima, and 23 (8.4%) from Spokane. Eleven serogroups, all within the currently available 23-valent pneumococcal polysaccharide vaccine, represented the majority (230, 83.6%) of the 275 isolates, including serogroups 14 (44, 16.0%), 9 (41, 14.9%), 6 (30, 10.9%), 19 (27, 9.8%), 4 (21, 7.6%), 23 (18, 6.5%), 22 (12, 4.4%), 12 (11, 4.0%), 18 (10, 3.6%), 1 (9, 3.3%), and 7 (7, 2.5%); 25 isolates (9.1%) could not be assigned to a serotype. The remaining 20 isolates belonged to one of the following serogroups: 3, 8, 10, 11, 13, 15, 16, 20, 31, 33, 38, and 29/35/42.

Susceptibility data are presented in Table 1. PNSP (MIC ≥0.1 µg/ml) accounted for 42 (15.3%) of the 275 isolates and included 4 (1.5%) penicillin-resistant pneumococci (PRP) (MIC ≥2 µg/ml). Serogroups 9 (10, 23.8%), 6 (9, 21.4%), 19 (9, 21.4%), 14 (7, 16.7%), and 23 (6, 14.3%) made up 41 (97.6%) of the 42 PNSP. Forty (95.2%) of the 42 PNSP isolates were nonsusceptible to at least one additional antimicrobial drug, 39 (92.9%) to TMP/SMX, 16 (38.1%) to erythromycin, 12 (28.6%) to imipenem, 10 (23.8%) to ceftriaxone, 9 (21.4%) to chloramphenicol, 1 (2.4%) to clindamycin, and 1 (2.4%) to rifampin. Thirty-three (12.0%) of the 275 isolates were susceptible to penicillin and nonsusceptible to one or more other antimicrobial drugs. There were no significant temporal differences in the prevalence of PNSP when the study period was divided into quartiles.

Seventy-five (27.3%) of the 275 isolates were nonsusceptible to at least one of the following drugs: TMP/SMX, penicillin, erythromycin, imipenem, ceftriaxone, chloramphenicol, clindamycin, and rifampin (Table 1). All 275 isolates were susceptible to vancomycin. Five serogroups (6, 23, 19, 9, 14) accounted for 67 (89.3%) of the 75 isolates nonsusceptible to at least one antimicrobial drug. Twenty (66.7%) of the 30 serogroup-6 isolates and 14 (77.8%) of the 18 serogroup-23 isolates were nonsusceptible to at least one antimicrobial drug. Thirteen (72.2%) of 18 serogroup-23 isolates and 18 (60.0%) of 30 serogroup-6 isolates were nonsusceptible to TMP/SMX, 7 (38.9%) of those solely to TMP/SMX.

Forty-seven (17.1%) of the 275 isolates were MDNSP. Serogroups 9 (8, 17.0%), 19 (9, 19.1%), 14 (8, 17.0%), 6 (13, 27.7%), and 23 (6, 12.8%) comprised 44 (93.6%) of the 47 MDNSP isolates. Forty (85.1%) of the 47 MDNSP were also PNSP (Table 1).

Demographic and risk factor data

Two hundred forty-seven (89.8%) patient medical records were available for data abstraction. Mean patient age was 48.2 years (range 1 day to 95 years). The majority of the enrolled patients were Caucasian adults with at least one underlying illness; the most common diagnosis was pneumonia (Table 2).

Fifteen (28.8%) of 52 patients ≤12 years of age were infected with MDNSP compared with 27 (13.8%) of 195 persons >12 years of age (RR 2.08; 95% CI 1.2–3.62). There were no statistically significant differences with regard to patient age and rate of resistance to individual antimicrobial drugs. There were also no statistically significant differences in either the proportion of nonsusceptible strains or serogroup distributions by geographic region.

Two variables were found by univariate analysis to be risk factors for infection with PNSP: immunosuppression and antimicrobial drug use in the month before admission.

TABLE 2.—*Demographic data for 247 patients with invasive pneumococcal infection*

Variable	*Value (%)*
Age (years)	
Mean (range)	48.2, 0.1–95
<2	35 (14.2)
2–12	17 (6.9)
13–40	34 (13.8)
41–64	70 (28.3)
≥65	91 (36.8)
Race	
Caucasian	115 (46.6)
African-American	14 (5.7)
Hispanic	1 (0.4)
Native American	8 (3.2)
Unknown	109 (44.1)
Sex	
Male	139 (56.3)
Female	107 (43.3)
Unknown	1 (0.4)
Payment source	
Medicare	87 (35.2)
Medicaid	50 (20.3)
Private insurance	87 (35.2)
Self-pay	6 (2.4)
Other or unknown	17 (6.9)
Admission diagnosis	
Pneumonia	140 (56.7)
Sepsis/bacteremia	24 (9.7)
Meningitis	7 (2.8)
Other	72 (29.2)
Unknown	4 (1.6)
Underlying illness	
Chronic lung disease	65 (26.3)
Diabetes	30 (12.1)
Chronic liver disease	25 (10.1)
AIDS ($CD4^+$ <500 cells/mm^3)	6 (2.4)
Immunosuppression	26 (10.5)
Splenectomy	5 (2.0)
At least one risk factor for *S. pneumoniae* infection*	194 (78.3)

*As defined by the CDC: age <2 or ≥65 years, chronic liver disease, chronic pulmonary disease, diabetes, splenectomy, or immunosuppressive conditions including HIV positivity, solid organ or bone marrow transplantation, neutropenia, and immunosuppressive drug therapy.

Nine of 26 (34.6%) immunosuppressed patients were infected with PNSP compared with 27 of 221 (12.2%) non-immunosuppressed patients (RR 2.83; 95% CI 1.5–5.35). Ten of 29 (34.5%) patients with a history of antimicrobial drug use the month before hospitalization were infected with PNSP compared with 26 of 211 (12.3%) patients not taking antimicrobial drugs (RR 2.88; 95% CI 1.55–5.34). Moreover, both immunosuppression and prior antimicrobial drug use were found by multivariate analysis to be significantly associated with infection with PNSP ($P < 0.01$ and $P < 0.02$, respectively). All other risk factors assessed (race; sex; insurance status; place of residence; alcohol or tobacco use; presence of underlying disease such as diabetes or chronic lung, renal, or liver disease; history of otitis media; or splenectomy) were not significantly related to infection with PNSP. The mean length of hospital stay for patients with a penicillin-sensitive organism was 5.7 days compared with 7.1 days for those with a nonsusceptible organism ($P = 0.47$). There was no significant difference between patients with penicillin-susceptible and penicillin-nonsusceptible isolates with respect to admission to an ICU, ICU length of stay, occurrence of complications such as requirement for mechanical ventilation or a hypotensive episode, or mortality.

Of the 247 patients whose records were available, 178 (72.1%) had evidence of clinical improvement (return of temperature to normal, decreased requirement for supplemental oxygen, or improved subjective status) upon hospital discharge, 29 (11.7%) did not show improvement, and 25 (10.1%) died. (The status of 15 (6.1%) patients was not documented.) Infection with PNSP was not associated with increased risk for lack of improvement or death.

Of the 247 patients whose records were available, 194 (78.5%) had at least one risk factor for *S. pneumoniae* infection as defined by the Advisory Committee on Immunization Practices (ACIP) (age <2 or ≥65 years; presence of chronic liver disease, chronic pulmonary disease, or diabetes; presence of an immunosuppressive condition; or splenectomy), and 160 patients (64.8%) were candidates for the 23-valent pneumococcal vaccine according to ACIP guidelines.[15] Receipt of the pneumococcal vaccine (before or during hospitalization or anticipated after discharge) was documented in the medical record for 12 (4.9%) patients.

Discussion

Drug-resistant strains of *S. pneumoniae* were relatively uncommon in the United States before the 1990s. Since then, increasing prevalence of drug-resistant organisms has been documented in numerous areas around the country.[3–6,16,17] The CDC pneumococcal sentinel surveillance system has shown an increase in both PNSP (from 6.6% to 14.1%) and PRP (from 1.3% to 2.2%) between 1992 and 1994 among invasive pneumococcal isolates collected from 13 hospitals in 12 states.[3,4]

Our study found the prevalence of PNSP to be 15.3% among isolates from 13 hospitals in Washington State, consistent with the CDC's most recent national surveillance study. This prevalence of PNSP is consistent with the suggestion that empiric treatment regimens for central nervous system (CNS) infections and life-threatening non-CNS infections caused by *S. pneumoniae* should include vancomycin in addition to an extended-spectrum cephalosporin.[18] The PRP prevalence of 1.5% in our study is lower than the national rate of 3.2% for invasive pneumococcal infections.[4] Rates of PRP in a community can increase dramatically within a short time.[6] In addition, rates of PRP may vary from hospital

to hospital, and increased proportions of PRP may exist in hospitals not represented in our study. The small proportion of penicillin-resistant isolates is encouraging, but continued local surveillance of invasive pneumococcal isolates throughout Washington State is recommended to look for increases in resistance rates that recent national and global resistance trends portend.[8,19]

Ninety-five percent of our PNSP and PRP isolates were MDNSP, while only 3% of the penicillin susceptible isolates were MDNSP. These data further support NCCLS recommendations to test the susceptibility patterns of all sterile-site isolates using the oxacillin disk diffusion screening followed by MIC testing for penicillin, as well as extended-spectrum cephalosporins and several other antimicrobial drugs that may be clinically indicated for treatment, such as erythromycin, tetracycline, TMP/SMX, vancomycin, and chloramphenicol.[14]

The majority of our study patients (56.7%) with invasive pneumococcal disease were admitted with a diagnosis of pneumonia. Treatment with intravenous penicillin G or other β-lactam drugs results in high serum concentrations that greatly exceed the current penicillin MICs.[20] In fact, available data suggest that bacteremic pneumococcal pneumonia caused by PNSP and treated with conventional β-lactam therapy does not result in increased mortality.[21] Although our study has limited power, we did not find infection with PNSP to be associated with increased morbidity or mortality. A conservative approach to β-lactam antimicrobial drug dosing (such as 2 to 4 million units of penicillin per adult dose) that will ensure concentrations above the MIC may be adequate in uncomplicated cases of non-CNS infection. Some authorities suggest using an extended-spectrum cephalosporin for severe PNSP infections.[22] For patients with β-lactam hypersensitivity, a macrolide, tetracycline, quinolone, or vancomycin is recommended depending on local resistance patterns.[20] Use of an extended-spectrum cephalosporin and vancomycin with or without rifampin has been recommended for empiric treatment of suspected PNSP meningitis.[18,23]

The results of this study are consistent with prior data demonstrating that use of antimicrobial drugs for treatment or prophylaxis is associated with antimicrobial drug resistance among *S. pneumoniae*.[24–27] An association between drug-resistant pneumococcal infection and immunosuppression has been reported previously.[28] We also found that immunosuppression was associated with drug-resistant *S. pneumoniae* infection independent of antimicrobial drug use in the past month. Possible explanations for this observation include an effect of long-term antimicrobial use among immunosuppressed patients or a dose-response relationship, with immunosuppressed patients receiving more courses of antimicrobial drugs or drugs that are more efficient at selecting resistant strains. More frequent hospitalization with nosocomial acquisition of PNSP may also be a reason for increased resistance rates among immunocompromised patients.

Five serogroups (9, 19, 14, 6, and 23) were represented among 97.6% of PNSP and 93.6% of MDNSP in our study, consistent with previous surveillance reports.[3,4] Not only are these five serogroups contained in the 23-valent pneumococcal vaccine, but the serogroups of 240 (87.3%) of the 275 isolates collected during this study are also included in the vaccine. In general, approximately 85%–90% of invasive pneumococcal infections in the United States are caused by one of the 23 capsular types found in the vaccine.[29]

Patients 2 to 12 years of age were more likely to be infected with PNSP and, along with patients ≤2 years of age, were more likely to be infected with MDNSP than patients >12 years. The 28.6% rate of resistance to at least one antimicrobial drug and the 16.5% rate of MDNSP in adults ≥65 years of age or older deserve emphasis, as consequences of treatment failure may be greater in the elderly.[4,5] For patients >60 years, the incidence of pneumococcal pneumonia is estimated to be 3 to 8 cases per 1,000 persons per year, a figure three times higher than that for younger adults. Ten to 30% of elderly patients with pneumococcal pneumonia will develop bacteremia and, despite appropriate antimicrobial treatment and intensive medical care, 30%–40% of elderly patients with pneumococcal bacteremia will die.[29] Case-control studies have shown that pneumococcal vaccination prevents invasive bacteremic disease in 56% to 81% of cases and may offer a more proactive approach for prevention of invasive pneumococcal infections.[29]

Of the 247 patients with available records, 194 (78.5%) were found to have at least one risk factor for infection with *S. pneumoniae* as defined by the CDC. Of those, 160 (82.5%) should have received the vaccine according to the ACIP guidelines,[29] but only 12 (6.2%) had medical record documentation of receipt of the vaccine before or during their hospital admission. Although medical record documentation is very likely a minimum estimate of vaccine utilization, this rate of vaccination is low, and measures previously recommended by the ACIP, such as standing orders for pneumococcal vaccination administration, standards for immunization record review, community immunization programs, joint administration with the influenza vaccine, and patient and provider education sessions to increase awareness of its benefits, should be encouraged.[29]

Acknowledgments

We thank Susan R. Swanzy, BS, RM (AAM); Sam Eng, MS, SM (AAM); and Mimi Gupta, MSc, for assistance in processing cultures; Greg Baumgardner, Sen Dimas, and Stephanie Prausnitz, MS, for assistance and advice with statistical analysis; Jonathan Sugarman, MD, MPH, for project guidance; Renee Kanan, MD, MPH, for assistance with hospital enrollment; Deena Uberuaga and colleagues at PRO-West for data abstraction from medical records; and staff at all participating hospitals for their cooperation with this research endeavor.

REFERENCES

1. Centers for Disease Control and Prevention. Increasing pneumococcal vaccination rates among patients of a national health-care alliance—United States, 1993. MMWR 1995; 44:741–744

2. Appelbaum PC. Antibiotic-resistant pneumococci—facts and fiction. J Chemother 1994; 6 (Suppl 4):7–15,23–24

3. Breiman RF, Butler JC, Tenover FC, Elliot JA, Facklam RR. Emergence of drug-resistant pneumococcal infections in the United States. JAMA 1994; 271:1831–1835

4. Butler JC, Hofmann J, Cetron MS, Elliott JA, Facklam RR, Breiman RF. The continued emergence of drug-resistant *Streptococcus pneumoniae* in the United States: an update from the Centers for Disease Control and Prevention's Pneumococcal Sentinel Surveillance System. J Infect Dis 1996; 174:986–993

5. Hofmann J, Cetron MS, Farley MM, Baughman WS, Facklam RR, Elliott JA, et al. The prevalence of drug-resistant *Streptococcus pneumoniae* in Atlanta. N Engl J Med 1995; 333:481–486

6. Duchin JS, Breiman RF, Diamond A, Lipman HB, Block SL, Hedrick JA, et al. High prevalence of multidrug-resistant *Streptococcus pneumoniae* among children in a rural Kentucky community. Pediatr Infect Dis J 1995; 14:745–750

7. Collignon PJ, Bell JM. Drug-resistant *Streptococcus pneumoniae*: the beginning of the end for many antibiotics? Australian Group on Antimicrobial Resistance (AGAR). Med J Aust 1996; 164:64–67

8. Garcia-Martos P, Galan F, Marin P, Mira J. Increase in high resistance to penicillin of clinical isolates of *Streptococcus pneumoniae* in Cadiz, Spain. Chemotherapy 1997; 43:179–181

9. Baquero F, Martinez-Beltran J, Loza E. A review of antibiotic resistance patterns of *Streptococcus pneumoniae* in Europe. J Antimicrob Chemother 1991; 28 (Suppl C):31–38

10. Levin AS, Teixeira LM, Sessegolo JF, Barone AA. Resistance of *Streptococcus pneumoniae* to antimicrobials in São Paulo, Brazil: clinical features and serotypes. Rev Inst Med Trop São Paulo 1996; 38:187–192

11. Pean Y, Goldstein FW, Guerrier ML. Highlights of the French Antimicrobial Resistance Surveillance Project. French Study Group. Diagn Microbiol Infect Dis 1996; 25:191–194

12. Paul J, Bates J, Kimari J, Gilks C. Serotypes and antibiotic susceptibilities of *Streptococcus pneumoniae* in Nairobi, Kenya. J Infect 1996; 32:139–142

13. Jernigan DB, Cetron MS, Breiman RF. Minimizing the impact of drug-resistant *Streptococcus pneumoniae* (DRSP). A strategy from the DRSP Working Group. JAMA 1996; 275:206–209

14. National Committee for Clinical Laboratory Standards. Performance standards for antimicrobial susceptibility testing, vol. 17. Villanova, PA, National Committee for Clinical Laboratory Standards, 1997

15. Centers for Disease Control and Prevention. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1997; 46:1–24

16. Reichler MR, Allphin AA, Breiman RF, Schreiber JR, Arnold JE, McDougal LK, et al. The spread of multiply resistant *Streptococcus pneumoniae* at a day care center in Ohio. J Infect Dis 1992; 166:1346–1353

17. Doern GV, Brueggemann A, Holley HP Jr, Rauch AM. Antimicrobial resistance of *Streptococcus pneumoniae* recovered from outpatients in the United States during the winter months of 1994 to 1995: results of a 30-center national surveillance study. Antimicrob Agents Chemother 1996; 40:1208–1213

18. Friedland IR, McCracken GH Jr. Management of infections caused by antibiotic-resistant *Streptococcus pneumoniae*. N Engl J Med 1994; 331:377–382

19. McCaig LF, Hughes JM. Trends in antimicrobial drug prescribing among office-based physicians in the United States. JAMA 1995; 273:214–219

20. Finch RG. Pneumonia: the impact of antibiotic resistance on its management. Microb Drug Resist 1995; 1:149–158

21. Pallares R, Linares J, Vadillo M, Cabellos C, Manresa F, Viladrich PF, et al. Resistance to penicillin and cephalosporin and mortality from severe pneumococcal pneumonia in Barcelona, Spain. N Engl J Med 1995; 333:474–480

22. Leggiadro RJ. The clinical impact of resistance in the management of pneumococcal disease. Infect Dis Clin North Am 1997; 11:867–874

23. Quagliarello VJ, Scheld WM. Treatment of bacterial meningitis. N Engl J Med 1997; 336:708–716

24. Nava JM, Bella F, Garau J, Lite J, Morera MA, Marti C, et al. Predictive factors for invasive disease due to penicillin-resistant *Streptococcus pneumoniae*: a population-based study. Clin Infect Dis 1994; 19:884–890

25. Doone JL, Klespies SL, Sabella C. Risk factors for penicillin-resistant systemic pneumococcal infections in children. Clin Pediatr 1997; 36:187–191

26. Bedos JP, Chevret S, Chastang C, Geslin P, Regnier B. Epidemiological features of and risk factors for infection by *Streptococcus pneumoniae* strains with diminished susceptibility to penicillin: findings of a French survey. Clin Infect Dis 1996; 22:63–72

27. Block SL, Harrison CJ, Hedrick JA, Tyler RD, Smith RA, Keegan E, et al. Penicillin-resistant *Streptococcus pneumoniae* in acute otitis media: risk factors, susceptibility patterns and antimicrobial management. Pediatr Infect Dis J 1995; 14:751–759

28. Garcia-Leoni ME, Cercenado E, Rodeno P, Bernaldo de Quiros JC, Martinez-Hernandez D, Bouza E. Susceptibility of *Streptococcus pneumoniae* to penicillin: a prospective microbiological and clinical study. Clin Infect Dis 1992; 14:427–435

29. Konradsen HB. Quantity and avidity of pneumococcal antibodies before and up to five years after pneumococcal vaccination of elderly persons. Clin Infect Dis 1995; 21:616–620

Epitomes

Important Advances in Preventive Medicine and Public Health

Preventive Medicine and Public Health

Peter Kerndt, MD

The Council on Scientific Affairs of the California Medical Association presents the following epitomes of progress in preventive medicine and public health. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, as to both scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in preventive medicine and public health that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Preventive Medicine and Public Health of the California Medical Association, and the summaries were prepared under the direction of Dr. Peter Kerndt and the panel.

New Vaccines for Infectious Diseases

A NEW VACCINE against rotavirus (RotaShield, Wyeth-Lederle) has recently been licensed by the FDA. Licensure is expected for a new vaccine against Lyme disease in early 1999. Both vaccines will pose challenges to clinicians in recommending their use.

Rotavirus is the most common cause of severe childhood diarrhea, and is estimated to cause 50,000 hospitalizations each year in the United States among children less than 5 years of age. The new rotavirus vaccine is a live, oral, tetravalent preparation with strains of rhesus monkey rotavirus (RRV-1), three of which contain genes from human rotavirus serotypes. Vaccination results in an immune response to the four human rotavirus serotypes most commonly responsible for rotavirus-associated diarrhea in infants and young children. Vaccine trials indicate the vaccine is 70%–95% effective against severe rotavirus diarrhea and is extremely effective in preventing hospitalization due to rotavirus diarrhea.

The recommended dose schedule is 2, 4, and 6 months of age. Initiation of vaccination after 6 months of age is not recommended. The recommended dose is 2.5 cc reconstituted from lyophilized powder packaged in individual dose bottles. The lyophilized vaccine can be stored at room temperature.

The principal adverse reaction to rotavirus vaccine is fever, which may occur within 3–4 days of vaccination. Since initial vaccination is recommended at 2 months of age, vaccine-associated fever may result in some infants receiving extensive evaluation for fever.

The $114 cost for the three-dose series makes this vaccine the least cost-effective childhood vaccine now in use. A positive benefit-to-cost ratio is achieved only when considering indirect savings from reduced societal costs such as lost parental work time. The vaccine will likely be covered by the national Vaccines for Children entitlement program, which provides free vaccines to underinsured and Medicaid-eligible children. Routine use of rotavirus vaccines is endorsed by the U.S. Public Health Service Advisory Committee on Immunization Practices.

Two new recombinant Lyme disease (LD) vaccines (LYMErix, SmithKline Beecham, and ImuLyme, Pasteur Merieux Connaught) have recently been developed based on the outer surface protein Osp-A of *Borrelia burgdorferi*, and have been found to be 76% and 92% efficacious, respectively, in large field trials. Licensure for LYMErix is imminent. The apparent mechanism of the vaccines is to prevent spirochete transmission during tick attachment and feeding.

Both vaccines are administered as a series of three intramuscular injections at 0, 1, and 12 months. Immunogenicity and efficacy were lower in persons who received only two doses and/or were over 60–65 years of age. Local reactions at the site of inoculation were reported in approximately 30% of vaccinees. To date, no safety or efficacy studies of LD vaccine have been done in children less than 15 years old, pregnant women, or immunocompromised individuals.

In the West, the vector of LD is the western black-legged tick, *Ixodes pacificus*. *I. pacificus* is most common in dense grassy or wooded areas, particularly in the northern coastal range and the western Sierra foothills of California. This species is uncommon in the Central Valley and south of the Tehachapi Mountains. The statewide proportion of *I. pacificus* infected with *B. burgdorferi* is comparatively low—approximately 2%–3% in adult ticks and 5%–6% in nymphs.

More than 85% of LD cases reported in the United States since 1982 are from the Northeast and Upper Midwest. The states with the greatest number of reported cases per 100,000 population in 1997 were Connecticut

(70.2), Rhode Island (44.6), and New York (18.3). The reported incidence in California and the Pacific region as a whole in 1997 was 0.5 cases per 100,000.

On the basis of the current information on vaccine efficacy and safety, and the known epidemiology of LD, the vaccine is *not indicated for routine use* in California residents. The vaccine may benefit some California residents who, through residence, occupation, or recreational activities, frequent areas with dense vegetation—particularly in the northern coastal range and western Sierra foothill regions—and regularly find ticks on their bodies and clothing. Persons who believe they are at elevated risk of LD should consult with their health care professional about the benefits and potential risks of vaccination.

Personal protective measures remain the most effective way to decrease the risk of all tick-borne diseases. These measures include avoiding areas with high tick populations, wearing appropriate clothing which limits tick access to the skin, using repellants, conducting self tick-checks, and promptly removing attached ticks.

STEVE WATERMAN, MD, MPH
Berkeley, California
CURTIS FRITZ, DVM, MPVM, PHD
Sacramento, California

REFERENCES

Tucker AW, Haddix AC, Bresee JS, Holman RC, Parashar, UD, Glass, RI. Cost-effectiveness analysis of a rotavirus immunization program for the United States. JAMA 1998; 279:1371–1376

Steere AC, Sikand VK, Meurice F, et al. Vaccination against Lyme Disease with recombinant *Borrelia burgdorferi* outer-surface lipoprotein A with adjuvant. NEJM 1998; 339:209–215

Steigbigel RT, Benach JL. Editorial: Immunization against Lyme Disease—an important first step. NEJM 1998; 339:263–264

New Tests for Detecting HIV Infection

THE ADVENT OF effective treatment to improve survival and quality of life for HIV-infected persons has increased the impetus for early diagnosis of HIV infection. In response to this need for early detection, several new testing methods have been developed that offer additional opportunities for convenient HIV screening.

Tests for HIV antibodies are the cornerstone of HIV screening. The enzyme linked immunosorbent assay (EIA) performed on serum collected by venipuncture has been widely used because it is readily available, inexpensive, and highly sensitive (sensitivity >99%, specificity >98%). If the EIA is negative, the laboratory reports a negative test result. If the EIA is repeatedly reactive, the laboratory performs a supplemental test (such as the Western blot or immunofluorescence assay) to confirm the positive test result.

HIV antibody tests that can be performed on oral fluids and on urine have recently been approved by the Food and Drug Administration (FDA) for professional use only in situations where it is difficult or impractical to obtain blood. The oral fluid test utilizes a specimen collection device (Orasure*, Epitope Inc, Beaverton, Oregon) to obtain antibody-rich transudate from the oral mucosa. The collection swab, which looks somewhat like a lollipop, is rubbed on the buccal mucosa, left in place for 2 minutes, and then placed in a preservative for transport to the laboratory. The swab is simple to use, painless, and eliminates the risk of occupational exposure to HIV. Both an EIA and Western blot can be performed on oral fluid specimens, with accuracy equivalent to that of serum testing (sensitivity and specificity of combined assays >99%).

The urine EIA for HIV antibodies (Sentinel HIV-1 Urine EIA, Seradyn Inc., Indianapolis, Indiana) has been available for several years, but its use was limited by the lack of a confirmatory test until earlier this year when the urine Western blot test received FDA approval. The urine HIV test may be especially useful in situations where urine but not blood is routinely collected, such as in drug treatment centers. However, the sensitivity and specificity of the urine test are slightly reduced compared with testing serum or plasma (99.1% and 90.1%, respectively), and both false negatives and false positives will occur more often.

And what about the much-publicized "home" HIV test? These kits, sold directly to consumers, are collection devices only to be used with blood specimens. The individual obtains a finger stick blood sample on filter paper that is mailed to a laboratory and tested by EIA, with immunofluorescent assay to confirm a reactive EIA. Accuracy is equivalent to other serum HIV tests. Results and counseling are provided by telephone. Sales of these tests are reportedly less than expected, and only one such product remains on the market.

Disadvantages common to all EIAs arise from their requirements for complex laboratory equipment and highly skilled personnel. The tests are usually run in batches, and results often are not available for 1 to 2 weeks. This may create a serious problem, because experience has shown that many persons do not return to learn their test results. Rapid assays to detect HIV antibody have been developed that can be performed one specimen at a time in an average of 10 minutes by less highly-trained individuals. The sensitivity of rapid assays is comparable to EIA. Therefore, a negative rapid test does not require further testing, and negative results with result-specific counseling can be provided at the initial visit. As with all other HIV screening tests, a reactive rapid test needs to be confirmed by a supplemental test, such as the Western blot. Persons whose rapid test is reactive can be counseled about their likelihood of being infected with HIV, but they must return for definitive results. Studies have shown that many more persons return for confirmatory results and counseling when they receive a preliminary positive result than when no result is provided until after confirmatory testing.

Currently, the Single Use Diagnostic System for HIV-1 (SUDS, Abbott-Murex, Norcross, Georgia), is the only FDA approved rapid test commercially available in the United States. SUDS uses plasma or serum and therefore requires venipuncture, a centrifuge, and a laboratory cer-

*Use of trade names is for identification only and does not imply endorsement by CDC or the US Department of Health and Human Services.

tified under the Clinical Laboratory Improvement Act (CLIA) to perform tests of moderate complexity. Numerous other rapid tests are widely used internationally that are simple to perform and use whole blood from a finger stick specimen or even oral fluids. Several of these are being evaluated in the United States and have been submitted for FDA approval. Once available, such tests will greatly facilitate HIV screening among persons in hard to reach at-risk populations.

One note of caution: the current oral fluid, urine, and rapid tests detect only HIV type 1. A small number of cases of HIV-2, endemic in parts of West Africa, have been detected in the United States. Routine testing for HIV-2 is recommended only for blood centers, but should also be considered for persons who may have been exposed to HIV-2, or when there is a clinical suspicion of HIV disease but a negative test for antibodies to HIV-1.

Since unrecognized HIV infection remains a major problem with important individual and public health implications, augmented testing can be invaluable in helping to identify and target the large number of persons who are unaware of their HIV status. The potential benefit from employing innovative, user-friendly methods may be enormous.

THERESA A. WOEHRLE, MD, MPH
Los Angeles, California
BERNARD BRANSON, MD, CDC
Atlanta, Georgia

REFERENCES

Centers for Disease Control and Prevention. HIV counseling and testing using rapid tests—United States, 1995. MMWR 1998; 47:211–215

Abramowicz, M. Diagnostic Tests for HIV. Med Lett Drugs Ther 1997; 39:81–83

Kassler W, Dillon B, Haley C, Jones W, Goldman A. On-site rapid testing with same day results and counseling. AIDS 1997; 11:1045–1051

Hepatitis C

HEPATITIS C HAS been called the "silent epidemic." This silence can refer to the silent nature of its clinical course, to the fact that over half of the 4 million chronically-infected persons in the United States are unaware of their status, and to the lack of a public health response to the epidemic. Approximately 30,000 acute new infections are estimated to occur each year. Over 75% of patients with acute hepatitis C will develop chronic infection, which can be associated with chronic hepatitis, end-stage liver disease, and hepatocellular carcinoma. Currently, chronic hepatitis C is responsible for an estimated 8,000–10,000 deaths annually in the United States, and without effective intervention that number could triple in the next 10–20 years. Hepatitis C is now the leading reason for liver transplantation in the United States.

The prevalence of chronic hepatitis C virus (HCV) infection varies in the population on the basis of risk factors for infection. In the United States, this ranges from 60%–90% of persons with hemophilia, 50%–90% of injection drug users, 10%–20% of hemodialysis patients, 4%–15% of persons with a history of sexually-transmitted diseases, 9% of persons with more than 50 sex partners (lifetime), 6% of persons transfused before 1990, 1.8% of the general population, to 0.3% of volunteer blood donors.

The risk of HCV transmission from perinatal, sexual, and non-sexual household exposure is uncertain but low, while that from blood transfusion is no longer significant. Illegal (primarily injection) drug use currently accounts for 60% of HCV transmission in the United States, and also accounted for a substantial proportion of HCV infections in the past. Many persons with chronic HCV infection may have acquired their infection 20 to 30 years ago as a result of occasional experimentation with illegal drug injection.

The silence of public health agencies in regard to hepatitis C will soon be broken. Driven in part by the decision of the US Department of Health and Human Services to notify selected past recipients of blood transfusions of their risk, the Centers for Disease Control and Prevention, together with state and local health departments, are developing a national public health strategy. This strategy will be based on the identification, counseling, testing and referral of persons at risk for HCV infection. Screening will be recommended for specific groups based on their risk for infection. It is anticipated that large numbers of patients will be referred for medical evaluations. It will be of increasing importance for health care professionals to be able to evaluate and manage hepatitis C.

The natural history of chronic hepatitis C is highly variable, and some individuals may have a relatively benign outcome without significant liver disease. However, the risk of developing significant hepatic fibrosis, liver failure and hepatocellular carcinoma increases with time such that in the first 20 years of infection, 10%–20% of patients will develop cirrhosis, with alcohol consumption being an important risk factor.

Most patients are asymptomatic or have non-specific symptoms of fatigue. In some patients, extrahepatic disease such as cryoglobulinemia, glomerulonephritis or mucocutaneous vasculitis is present. Patients are usually diagnosed with HCV based upon the finding of anti-HCV by enzyme-linked immunosorbent assay (EIA) during evaluation for serum aminotransferase elevation or a history of one or more risk factors; or as a result of screening for blood donation. Recombinant immunoblot tests (RIBA) can be used to confirm anti-HCV reactivity, but testing for HCV RNA in serum by reverse-transcriptase polymerase chain reaction (PCR) is a more direct approach to discriminating between chronic infection and false positive antibody tests or previous infection. Unfortunately, commercial tests for HCV RNA by PCR are not yet standardized and some may not be reliable. Serum ALT elevation is the most common liver test abnormality in chronic hepatitis C infection, but 30%–50% of patients have normal ALT values despite detectable HCV RNA and abnormal liver histology.

The management of patients with chronic hepatitis C includes counseling regarding infectivity and abstention from alcohol consumption, vaccination against hepatitis

A and B if indicated, and evaluation for treatment and screening for hepatocellular carcinoma. Alpha interferon (α-IFN) therapy results in virological response in 40% to 50% of patients treated for 12 weeks, and responders should be maintained on treatment for at least one year. The current goal of therapy is sustained virological response (defined as non-detectability of HCV RNA by PCR for at least 6 months after treatment is discontinued) which is associated with marked improvement in hepatic histology and may indicate viral eradication. Recent trials of ribavirin added to α-IFN have demonstrated significantly higher on-treatment and sustained virological response rates compared to α-IFN monotherapy. However, patients must be carefully selected for treatment with these agents, because of potential side effects, and because therapy has not demonstrated effectiveness in patients with normal ALT levels. Prior to treatment, liver biopsy should be performed for staging of the disease.

Patients with decompensated liver disease are not candidates for therapy and should be referred early for liver transplantation evaluation. Although guidelines for screening for hepatocellular carcinoma have not been established, hepatic ultrasound and serum alpha-fetoprotein tests should be done during baseline evaluation of all patients, and follow-up testing performed, particularly in patients with cirrhosis.

Hepatitis C is an important viral infection with serious disease implications. Over the past decade, significant strides have been made in the field of hepatitis C with identification of the virus, development of effective therapies and definition of the epidemiology of the infection. Further research on the pathogenesis and treatment of hepatitis C is clearly necessary.

KAREN L. LINDSAY, MD
Los Angeles, California
JON ROSENBERG, MD
Berkeley, California

REFERENCES

McQuillan GM, Alter MJ, Moyer LA, Lambert SB, Margolis HS. A population based serologic study of hepatitis C virus infection in the United States. In, Rizzetto M, Purcell RH, Gerin JL, Verme G, (Eds): Viral Hepatitis and Liver Disease. Turin, Italy, Edizoni Minerva Medica, 1997; pp 267–270

National Institutes of Health Concensus Development conference: management of hepatitis C. Hepatology 1997; 26 (Suppl 1):S1–S156

McHutchinson J, Gordon S, Schiff ER, et al, for the Hepatitis Interventional Therapy Group. Interferon alfa-2b monotherapy versus interferon alfa-2b plus ribavirin as initial treatment for chronic hepatitis C: results of a U.S. multi-center randomized controlled trial. N Engl J Med 1998; 339:1485–1492

Indoor Environmental Quality

INDOOR ENVIRONMENTAL QUALITY is a relatively new concept that includes the older concerns for indoor air quality, building-related illness and "sick building syndrome," but expands this to include ergonomic issues (lighting, noise, furniture) and psychological issues (decision latitude, stressful working conditions, and job satisfaction). Major recent advances in indoor environmental quality have occurred in several areas, including recognition of the significance of workplace passive smoking, new methods of measurement of airborne microorganisms along with greater recognition of their importance as risk factors for disease, and new application of more sensitive epidemiologic methods to building investigations.

Perhaps the greatest recent improvements in indoor environmental quality are the result of widespread recognition of the harmful effects of workplace passive smoking. A recent meta-analysis found an odds ratio or relative risk of development of lung cancer among nonsmokers exposed to environmental tobacco smoke at work to be 1.39 (95% confidence interval 1.15–1.68). This latest meta-analysis refuted five error-studded industry-sponsored meta-analyses published in 1994 that found no relationship between lung cancer and environmental tobacco smoke in the workplace. Clinically, inquiry into environmental history should include not simply whether a patient is a current or former smoker, but also whether the patient has been significantly exposed to environmental tabacco smoke.

Disease-causing mold and other airborne microorganisms as risk factors for illness among both adults and children are another focus of efforts to improve indoor environmental quality. Several recent cases have demonstrated the adverse impact such organisms may have on building occupants. Courthouse workers in Florida complained of mucous membrane irritation, fatigue, headache and chest tightness in association with roof and window leaks and building contamination with *Stachybotrys chartarum* and *Aspergillus versicolor.* In a well-publicized outbreak, a geographic cluster of 10 cases of pulmonary hemorrhage and hemosiderosis occurred among infants living in homes in Cleveland, Ohio with toxigenic *Stachybotrys atra* and other fungi in the indoor air. In addition, several cases of suspected hypersensitivity pneumonitis have been diagnosed in health spa workers where *Mycobacterium avium* was subsequently cultured from the environment.

New methods of measurement of airborne microorganisms, along with the application of more sensitive epidemiological methods to building investigations, now make it possible to more efficiently identify organisms responsible for deleterious health effects. The application of DNA polymerase chain reaction (PCR) coupled to an enzymatically generated color reaction allows direct detection of airborne *M. bovis* Baccillus of Calmette-Guerin (BCG), a surrogate for pathogenic *M. tuberculosis.* Analysis can be completed in less than 1.5 days, in contrast to traditional culture methods requiring a minimum of 2–3 weeks. The *M. bovis* test is currently in use by researchers. It may lead to the development of a specific test for *M. tuberculosis* in the future, using similar technology.

A cluster of building-related illnesses was found among safety personnel working in a medium sized government office building localized to a basement with history of sewage overflows. The outbreak was confirmed by two measures of spatial clustering: The number of ill workers working in adjacent offices and

the mean distance from a geographic center of the cases. This method was found to be a sensitive way to identify a subset of workers in a distinct location within a building at increased risk, despite the building having overall a relatively reduced frequency of symptoms compared with usual rates in non-problem buildings.

These cases illustrate the increasing concern and awareness of the effects of the indoor environment on health.

JAMES E. CONE, MD, MPH
San Francisco, California

REFERENCES

Wells AJ. Lung cancer from passive smoking at work. Am J Public Health 1998; 88:1025–1029

Linz DH, Pinney SM, Keller JD, White M, Buncher CR. Cluster analysis applied to building-related illness. J Occ Env Med 1998; 40:165–171

Seltzer JM: Biologic contaminants. In Seltzer JM (Ed): Occupational Medicine: State of the Art Reviews: Effects of the Indoor Environment on Health. Philadelphia, Pa, Hanley and Belfus, 1995, Vol 10, pp 1–25

Hodgson MJ, Morey P, Leung W-Y, et al. Building-associated pulmonary disease from exposure to Stachybotrys chartarum and *Aspergillus versicolor*. J Occ Env Med 1998; 152:757–762

Update on Public Health in Correctional Facilities

Public health interventions in correctional facilities are insufficient. For example, 33% of state and federal prisons conduct mandatory screening for human immunodeficiency virus (HIV) but only 59% provide voluntary testing upon inmate request, although the prevalence of HIV infection in state and federal prisons is 1% to 20%. A recent serosurvey of incoming inmates at six California reception centers demonstrated an HIV prevalence rate of 2.5%. In addition to the lack of data about prevalence, there are no data that identify how many HIV infected persons in prisons or jails receive appropriate anti-retroviral therapy. Inmates coming into prison do seem to be aware of the potential for HIV acquisition. Although incoming inmates may understand that sharing needles and sexual intercourse could result in transmission of HIV, once in prisons, educational programs and prevention efforts are often lacking.

Coinciding with the advent of the HIV epidemic, rates of tuberculosis (TB) rose dramatically. In 1994, 4.6% of reported new tuberculosis cases were diagnosed in residents of correctional facilities. Despite this, some correctional facilities still do not follow current Centers for Disease Control and Prevention guidelines regarding TB screening. For correctional facilities that provide some form of TB control, there are no published data on the effectiveness of these programs.

Universal screening programs in jails for syphilis, gonorrhea and chlamydia have proved effective in diagnosing and treating large numbers of individuals for these sexually transmitted diseases. Universal screening of inmates for syphilis and gonorrhea at one midwest county jail demonstrated syphilis rates of 2.7% for males and 10.4% for females, and gonorrhea rates of 1.5% for males and 4.3% for females. Linkage to local health departments facilitates treatment of these individuals. Despite the opportunity for screening and treating sexually transmitted diseases in jails, this practice is not routinely practiced elsewhere.

Rates of hepatitis B infection in the incarcerated population range from 19% to 44%, a rate consistent with high prevalence of risk factors associated with hepatitis B infection. Despite these data, the author is aware of only two state prison systems that routinely screen and vaccinate all incoming inmates against hepatitis B infection.

Since hepatitis C testing became available, significant numbers of incarcerated persons have been identified with hepatitis C infection. A recent seroprevalence study at 6 California prison intake reception centers revealed that 41% of 5144 individuals screened were positive for hepatitis C antibodies. Unfortunately, interventions are not universally endorsed and are notably expensive.

The prevalence of smoking among incarcerated individuals may exceed 80%, yet by 1997 only 13 states were either smoke free or transitioning to a smoke-free environment. Despite civilian laws in many states that mandate smoke-free environments for workers and occupants of public buildings, prisons and jails have been slow to change. Inmates who do not smoke may be required to live with persons who do smoke without opportunities for non-smoking housing assignments. Individuals who work with inmates (correctional officers, social workers, and health care workers) are similarly subjected to environmental tobacco smoke.

Possibly due to a paucity of weapons (especially guns), homicide rates in prisons are about half the civilian homicide rate. Yet, homicide is the leading cause of premature death for youths paroled from prison and as many as 44%–67% of homicide victims have a prior criminal record or were on parole at the time of death. Despite the significant degree of violence affecting this population, few violence prevention programs exist in United States correctional facilities.

Physicians working in correctional environments must be aggressive in taking advantage of opportunities to address under-treated conditions that have effective therapies. For behavior-based public health problems such as smoking and violence, physicians can advocate for change and investigate other intervention strategies. For conditions such as hepatitis C, with evolving diagnostic and treatment recommendations, physicians should be prudent in developing policies.

MICHAEL PUISIS, DO
Albuquerque, New Mexico

REFERENCES

Vlahov D. Epidemiology of HIV infection. In M Puisis (Ed): In Clinical Practice in Correctional Medicine St. Louis, Missouri, Mosby, 1998 pp 134–139

Agency Report: Seroprevalence of HIV, Hepatitis B, Hepatitis C, and Risk Behaviors Among Inmates Entering the California Correctional System. Los Angeles, California, California Department of Health Services, Office of AIDS, HIV/AIDS Epidemiology Branch, 1996

May J, Lambert W. Preventive health issues for individuals in jails and prisons In M Puisis (Ed): Clinical Practice in Correctional Medicine. St. Louis, Missouri, Mosby, 1998 pp 259–274

Acute Effects of Exposure to Methyl Tert-butyl Ether in Gasoline

OXYGENATED OR REFORMULATED gasoline is mandated by the Environmental Protection Agency to reduce ambient concentrations of carbon monoxide and ozone in heavily polluted areas. The most widely used gasoline oxygenate is methyl tert-butyl ether (MTBE), even though its use has resulted in widespread complaints of acute adverse health effects. The introduction of MTBE in Alaska in 1992 was accompanied by anecdotal reports from the general public of eye and respiratory tract irritation, headache, dizziness, nausea, and other non-specific symptoms. Preliminary surveys of populations in Anchorage and Fairbanks, conducted in the wake of media coverage of these alleged health effects and of public dissatisfaction with the high cost of the new fuel blended with MTBE, suggested that populations more heavily exposed to vehicular exhaust (all of which contained MTBE in those cities) had more symptoms. Based on these results, MTBE use was suspended in Alaska. Since then, the introduction of MTBE has been accompanied by complaints of acute health effects in Montana, New Jersey, Wisconsin, Maine, North Carolina, and Colorado. Groups opposing MTBE are active in several states. The state of California has recently undertaken a review of studies of acute symptomatic effects of MTBE, and of the possible carcinogenic and other chronic effects of MTBE in air and in ground water.

Several types of studies have been conducted to examine further the acute effects of MTBE exposure. Volunteers experimentally exposed to MTBE in three studies at concentrations up to 50 parts per million (ppm) did not report an increase in symptoms, although this exposure is higher than the maximum occupational exposures of 12 ppm (43.5 mg/m^3) measured in automobile-repair garages. However, experimental exposure to 75 ppm was recently reported to be associated with non-specific affective symptoms and irritation of mucus membranes. MTBE has been used therapeutically to dissolve stones in the biliary tract through direct injection, resulting in mean blood concentrations of 40,000 µg/liter, two to three orders of magnitude greater than concentrations observed in the blood of occupationally exposed workers. Although side effects, including nausea, central nervous system depression, and mild bronchitis have developed in rare instances as a complication of this procedure, in general these heavy exposures have been well-tolerated. These studies provide only equivocal evidence that acute adverse effects result from MTBE exposure. However, ambient exposure is likely to involve not only MTBE, but also its combustion and oxidation products, and other components of gasoline. Epidemiological studies of workers and of communities exposed to ambient concentrations of this mixture have not been totally consistent. A series of these studies in Alaska, Connecticut, New Jersey, Wisconsin, and Finland have examined acute symptoms and have, in general, also found inconsistent evidence for an association of these symptoms with environmental MTBE exposure. Only two epidemiologic studies have measured blood levels of MTBE. In these, automobile repair workers in the highest quartile of exposure were found to have more acute symptoms than other workers, but differences achieved statistical significance ($P < 0.05$) in only one. Unfortunately, potential bias resulting from self-selection among these workers limited the conclusions that could be drawn.

Studies of acute effects of MTBE exposure have not examined potentially sensitive populations with underlying respiratory disease. This is somewhat surprising, since exposure to air pollution is known to exacerbate symptoms among asthmatic patients. In addition, recent studies suggest that residential proximity to major roadways may contribute to the prevalence and severity of asthma in children. Combustion products of gasoline formulated with MTBE include respiratory irritants and respiratory sensitizers such as formaldehyde.

The acute effects of combustion products and atmospheric chemistry of gasoline, and of gasoline formulated with ethanol, as well as with MTBE, deserve further study within the context of sensitive populations. Controlled experimental exposures of patients with asthma to the combustion products of different formulations of gasoline would help identify relative hazards of different formulations. Appropriate epidemiological studies might examine the health effects of residential proximity to heavy traffic among children with asthma in communities with different mixes of gasoline. The possible role of MTBE as a carcinogen also requires prompt evaluation and possible regulatory action.

ROB McCONNELL, MD
ROBERT TABER, MD, MPH
Los Angeles, California

REFERENCES

The Potential Health Effects of Oxygenates Added to Gasoline. A Review of the Current Literature. Cambridge, Mass, Health Effects Institute, 1996

Hakkola M, Honkasalo ML, Pulkkinen P. Changes in neuropsychological symptoms and moods among tanker drivers exposed to gasoline during a work week. Occup Med 1997; 47(6):344–348

Leikauf GD, Kline S, Albert RE, Baxter CS, Bernstein DI, Buncher CR. Evaluation of a possible association of urban air toxics and asthma. Environ Health Pers 1995; 103(Suppl 6):253–271

White MC, Johnson CA, Ashley DL, Buchta TM, Pelletier DJ. Exposure to methyl tertiary-butyl ether from oxygenated gasoline in Stamford, Connecticut. Arch Environ Health 1995; 50:183–189

Motor Vehicle Occupant Protection for Children

MOTOR VEHICLE CRASHES remain a leading cause of death and injury for US children, despite improved crashworthiness of vehicles and effective restraint systems for children of all ages, including those with special health care needs. According to the Fatal Analysis Reporting System and General Estimates System, 1811 children aged 0–15 years sustained fatal injuries and

305,000 were non-fatally injured in motor vehicle crashes in 1996.

In the last two decades, with implementation of mandatory restraint-use laws, overall rates of death and injury have decreased. Yet, non-use remains the major risk factor for death and injury to children. Non-use increases with increasing age of the child. Driver use is the strongest predictor of child restraint use. Even adults who are conscientious about using restraints, however, may be unaware of the dangers posed by improper restraints and of how to select proper restraints.

Occupant protection for 4–9 year old children in particular needs to be targeted. Booster seats are essential for correct seat belt fit for children in this age group weighing 40–80 pounds. Multiple studies have documented that these children are frequently placed prematurely in seat belts without booster seats. A 1995 National Highway and Transportation Safety Administration study of observed child restraint use found that only 6% of the children weighing 40–80 pounds were in booster seats, while 75% were in seat belts.

"Safe vehicular packaging" for children requires occupant protection systems based on child anatomy and development. Restraints for children must be adjustable to accommodate the changing dimensions and behavioral characteristics occurring with growth and development. Salient features of child development relevant for occupant protection include rapid changes in weight, height and body proportions. Infants and young children have a disproportionately large head, with a high center of gravity and weaker neck structures resulting in relatively poor head support, combined with a soft, pliable skull that is less protective of the intracranial contents, and cartilaginous cervical vertebrae with slow replacement by bone. As a result, special consideration must be given to protecting children from skeletal and facial injuries that can occur even in low-speed collisions, resulting in long-term disruption of growth plates and subsequent abnormal growth. Protection from head injuries is also critical.

The abdominal organs, liver, spleen, and kidneys of children are less protected by the rib cage compared to the adult, and the bladder is less protected by the bony pelvis. The anterior superior iliac spines, the anchor points for the adult seat belt, must be sufficiently developed for proper and secure positioning. Behavioral characteristics of the child, such as the inability to sit still and erect for a sustained period of time often result in the child altering the fit or maneuvering out of the system altogether.

Adult belts have the potential to ride up over and directly load the abdomen. Then the child is at risk for flexing over the belt in a crash and the pelvis submarining under the belt. This could result in the seat belt syndrome—a spinal fracture, (usually lumbar or sacral) with an internal abdominal injury, related to compression of internal abdominal organs and hyperflexion of the spine over the belt system. Lap/shoulder belts may be similarly problematic. The cervical seat belt syndrome—fractures or fracture-subluxations of the proximal cervical spine with or without head injuries—may result from hyperflexion of the neck over a secured torso. The buckle of the lap/shoulder belt may sit high against the child's abdomen and slide up during a collision, increasing the chance of submarining under the belt. The shoulder portion of the belt may not sit on the shoulder, but rather lie against the child's neck, or may be placed behind the child, disrupting the optimal function of the restraint system.

The best child safety seat for each child is that which is easy to use, fits the vehicle seats and seat belt system, and is appropriate for the child's size and development. Given the array of available child safety seats, potential incompatibilities between the seat and the vehicle, and recommendations for children by age, size, and developmental characteristics, selecting the proper child safety seat has become a highly specialized technical field. Certified *child safety seat specialists*, available across the country, have the special expertise to advise and assist parents in selecting and properly using child restraint systems. The Department of Transportation Auto Safety Hotline (800-424-9393), Web Site htpp:\\www.nhtsa.dot.gov), local health care agencies, local hospitals, and law enforcement agencies are sources of information for families. The American Academy of Pediatrics has a wealth of materials on child occupant protection, including their *1998 Family Shopping Guide to Car Seats.*

The American Academy of Pediatrics guidelines recommend that the child should be placed in the belt-positioning booster seat as long as he/she fits. After 8 years of age and 60–80 pounds, a child can use the adult lap/shoulder belt *only* if it fits properly, but it is preferable to use a booster seat as long as possible. The back seat is the safest seat location for children of any age. The shield booster seat using the lap belt did not meet crash testing in the 6-year-old dummy test and should not be used, although it may be the only option. However, shield boosters may be the only option for vehicles with only lap belts. (A rear-facing child safety seat must never be placed in an airbag-equipped front passenger seat; out-of-position and unrestrained children in this location are also at risk for airbag-related injuries). Those providing health care for children are in a unique position to influence injury-preventive behaviors and therefore must be aware of the latest recommendations for child occupant protection.

PHYLLIS AGRAN, MD, MPH
DIANE WINN, RN, MPH
CRAIG ANDERSON, DHSc, PhD
Irvine, California

REFERENCES

Agran PH, Winn DG, Anderson CL. Child occupant protection in motor vehicles. Ped Rev 1997; 18:413–423

American Academy of Pediatrics Policy Statement. Selecting and using the most appropriate car safety seats for growing children: Guidelines for counseling parents. Pediatrics 1996; 97:761–762

Asthma—The Shift from Episodic Treatment to Ongoing Prevention, Education, and Management

ASTHMA IS A major public health problem in our society, affecting 14 to 15 million people in the United States. Morbidity is highest in children, blacks, and lower income and inner-city populations. Death rates are highest in older patients and blacks. Self-reported asthma prevalence and asthma death rates have increased, but the underlying reasons are uncertain.

Despite these trends, recent advances have improved our general understanding of asthma and our ability to manage it effectively. Asthma is now viewed as a chronic inflammatory disease requiring preventive management, as opposed to an episodic disease requiring intermittent acute treatment. To close gaps that exist between current science and actual practice in the community, the National Institutes of Health National Asthma Education and Prevention Program published *Guidelines for the Diagnosis and Management of Asthma.* These guidelines, updated in 1997, emphasize environmental controls, preventive medications, and ongoing education in the clinical management of asthma. A 52-page *Practical Guide* provides clinicians with suggestions and tools to use in their own practices.

Clinicians must work with patients and families to develop a workable plan to avoid and control precipitating factors. Patients should identify and avoid factors that worsen their disease, including allergens (such as dust mites, pets, and mold); irritants (such as tobacco and wood smoke); sulfites; and excessive exertion during high-pollution days. For example, using allergen-impermeable mattress and pillow covers and weekly hot water washing of sheets and blankets can decrease dust-mite allergen levels. Decreasing indoor humidity can also decrease both dust mites and indoor mold. Persons with persistent asthma should have skin or *in vitro* testing (e.g., radioallergosorbent (RAST) tests) for sensitivity to allergens to which they are perennially exposed. The test result should be used in the context of each patient's clinical history and may help motivate the patient to take appropriate control measures.

The guidelines explain how to grade severity of asthma, based on symptoms and objective measurements, into four categories: mild intermittent, mild persistent, moderate persistent, and severe persistent. Patients with any level of persistent asthma are advised to receive an annual influenza vaccine and use long-term preventive controller medications. These include inhaled steroids, cromolyn sodium, nedrocromil, long-acting beta$_2$-agonists, methylxanthines, and the new leukotriene modifiers. Inhaled steroids appear to be the most effective controller medications due to their potent anti-inflammatory actions. They are generally well tolerated and safe when used as recommended. To reduce the risk of potential side effects, patients using inhaled steroids should always use spacers and rinse their mouth after use. Other long-term control medications, such as the long-acting beta$_2$-agonists, can be added to achieve control while minimizing the inhaled steroid dosage. The exact role of leukotriene modifiers is still evolving. In infants and children with mild persistent asthma, cromolyn and nedocromil are often used initially due to their high safety profile. Although not first-line drugs, methylxanthines may be useful adjuncts for some patients, particularly for nocturnal symptoms, but require monitoring for potential toxicity.

Although proper inhaler technique and adherence to the medication schedule are important, it is estimated that only about half of patients adhere to their medication regimen and over half don't use their inhaler properly. Ongoing, consistent asthma education can potentially improve adherence and inhaler skills. Providing a full comprehensive educational session within the time span of a normal office visit is difficult; therefore, education should be incorporated into every encounter, including routine visits, urgent care visits, and when refilling prescriptions. Instructions should be repeated during regular follow-up visits, which are recommended every 1 to 6 months, depending on asthma severity and need for follow-up.

Treatment goals and plans should be made jointly by the patient, family, and physician and be tailored according to the patient's needs, lifestyle, and cultural beliefs. Patients should receive a *written* asthma action plan, explaining when they should adjust medications and seek medical help; this will facilitate early recognition and treatment of exacerbations and timely communication between the patient and clinician. Referrals to asthma classes and case management can be useful adjuncts. Overall, patients should be empowered with the tools to take control of their asthma in order to enjoy an active lifestyle.

Publications from the National Asthma Education and Prevention Program can be ordered through the National Heart, Lung and Blood Institute Information Center, P.O. Box 30105, Bethesda, MD 20824-0105 (Phone: 301-251-1222). Publications are also available on the Internet at http://www.nhlbi.nih.gov/nhlbi/lung/lung.htm.

EILEEN G. YAMADA, MD, MPH
Oakland, California

REFERENCES

National Asthma Education and Prevention Program. Guidelines for the Diagnosis and Treatment of Asthma, Expert Panel Report II. Bethesda, Maryland, National Institutes of Health, National Heart, Lung and Blood Institute, 1997

Barnes PJ, Pedersen S, Busse WW. Efficacy and safety of inhaled corticosteroids: new developments. Am J Respir Crit Care Med 1998; 157:S1–S53

Clark NM, Bailey WC, Rand C. Advances in prevention and education in lung disease. Am J Repir Crit Care Med 1998; 157:S155–S167

Vinicor F. Diabetes mellitus and asthma: "twin" challenges for public health and managed care systems. Am J Prev Med 1998; 14:87–92

Influenza

Influenza has been responsible for pandemics and epidemics throughout history, with recorded cases dating as far back as 412 B.C. Abrupt onset of fever, myalgia, sore throat, nonproductive cough and severe malaise lasting several days are hallmarks of influenza infection.

Although mortality increases during influenza epidemics, it is generally due to bacterial pneumonia and complications of underlying cardiopulmonary and other chronic diseases. Those at highest risk for complications during influenza season include persons over 65; persons of any age with chronic pulmonary, cardiovascular, metabolic or renal disorders, hemoglobinopathy or immunosuppression; children and teens on long-term aspirin therapy; and pregnant women in the second or third trimester. In recent years there has been an increase in influenza-associated deaths in the United States, primarily occurring in those with immunosuppressive conditions such organ transplantation, HIV disease, and prematurity, as well as the growing population of persons aged 65 and older.

For influenza type A, at least 15 hemagglutinin (H) subtypes, and 9 neuraminidase (N) surface glycoprotein forms are known to exist among animals. Aquatic birds, particularly ducks, appear to be the primary host for influenza A viruses, since all subtypes can be found in them. From time to time, an avian strain crosses over to mammalian hosts, most commonly pigs and horses. Reassortment of human and avian influenza A genes in pigs results in novel viruses that may infect humans. Epidemiologists consider Central Asia to be the prime mixing ground and source of most recent pandemics. Until 1997 only two neuraminidase antigens (N1, N2) and three hemagglutinin antigens (H1, H2, H3) had been described in human infections. A novel strain of influenza A (H5, N1) was identified in Hong Kong in 1997 that was responsible for six deaths and tremendous concern among public health experts worldwide. No significant person-to-person spread occurred.

Each year the World Health Organization global program for influenza surveillance obtains and analyzes influenza strains for antigenic characteristics to assist in vaccine development for the coming season. Influenza vaccine is made from purified, egg-grown inactivated viruses and is composed of the three virus strains anticipated to be the predominant strains that will be in circulation, two of type A and one of type B. The decision of which strains to target is typically made in March, allowing vaccine manufacturers 6–7 months to produce vaccine supplies. A miscalculation could result in failure to include the predominant strain in the vaccine, leaving individuals unprotected; such was the case in the 1997–98 season, when the dominant influenza strain in North America was a new type A variant, A/Sydney/5/97 (H3N2). Recent work on live-virus vaccines grown in tissue culture and administered by intranasal spray has shown promise, but large-scale production is some time away.

In addition to targeting individuals at medical risk of complications, influenza vaccination is also strongly recommended in occupational settings. Care-givers of people at medical risk (i.e. hospital, outpatient, home care, nursing home, and chronic care employees) and members of households with high-risk individuals should be vaccinated. Persons who should *not* be vaccinated with inactivated influenza vaccine include those with known anaphylactic hypersensitivity to vaccine components such as eggs, and those with acute febrile illness.

Chemoprophylaxis or therapy with antiviral drugs is another option to supplement influenza vaccination. The antivirals currently available are effective only against type A influenza viruses and prevent illness, not infection. This allows an immune response to be mounted that may protect against reinfection with similar viruses. Antivirals (amantadine and rimantadine hydrochloride [rimantadine approved only for chemoprophylaxis in children, not therapy]) reduce the severity and duration of illness in adults if administered within 48 hours of illness onset. These drugs are not recommended for use after 48 hours of symptoms due to their lower efficacy. The dosage for both drugs is 5mg/kg/d up to 150 mg in 2 divided doses for children aged 1–9 yrs, and 100 mg bid for persons aged 10–65 years. For people over 65 years of age, the dose of amantadine is 100 mg/d or less while for rimantadine the dose can be from 100–200 mg/d. Treatment should be stopped within 24–48 hours after disappearance of symptoms. Though the two drugs are similar, 75% of rimantadine is metabolized by the liver, while 90% of amantadine is excreted unchanged. Both drugs and their metabolites are excreted by the kidneys. In healthy adults, a higher incidence of central nervous system side effects (anxiety, nervousness, lightheadedness, and difficulty concentrating) is reported with amantadine. Gastrointestinal side effects, such as nausea and anorexia, are infrequent for both drugs. However, among the elderly and persons with renal insufficiency, seizure disorders, or certain psychiatric conditions, use of amantadine may cause more serious side effects, such as delirium, seizures, agitation, hallucinations, and marked behavioral changes. Lowering the dosage usually reduces these side effects.

The Centers for Disease Control and Prevention (CDC) publishes periodic updates about influenza in the *Morbidity and Mortality Weekly Report*. State and local health departments disseminate information about local incidence, vaccine availability, and vaccination programs. Additional information can be obtained from the CDC through the Fax Information Service (888-232-3299), or World Wide Web at http://www.cdc.gov/ncidod/diseases/flu/fluvirus.htm

SANDRA GROSS-SCHULMAN, MD, MPH, RN
DAVID E. DASSEY, MD, MPH
LAURENE MASCOLA, MD, MPH
Los Angeles, California

REFERENCES

The Centers for Disease Control and Prevention. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1998; 47(RR-6):1–26

Pandemic influenza: confronting a re-emergent threat. Proceedings of a meeting. Bethesda, Maryland, 11–13 December 1995. J Infect Dis 1997; 176(Suppl. 1): S1–S90

Potter J, Stott DJ, Roberts MA, Elder AG, et al. Influenza vaccination of health care workers in long-term-care hospitals reduces the mortality of elderly patients. J Infect Dis 1997; 175:1–6

Belshe RB, Mendelman PM, Treanor J, et al. The efficacy of live attenuated, cold-adapted, trivalent, intranasal influenzavirus vaccine in children. N Engl J Med 1998; 20:1405–1412

ADVISORY PANEL TO THE SECTION ON PREVENTIVE MEDICINE AND PUBLIC HEALTH

RONALD HATTIS, MD
Advisory Panel Chair
Redlands

GEORGE W. RUTHERFORD III, MD
CMA Section President
University of California School of Public Health, Berkeley

PETER KERNDT, MD, MPH
Immediate Past Panel President
Los Angeles

RICHARD HART, MD
Loma Linda University

DAVID H. THOM, MD
Stanford University

MARC B. SCHENKER, MD, MPH
University of California, Davis

CHARLOTTE G. NEUMANN, MD, MPH
University of California, Los Angeles

ELIZABETH BARRETT-CONNOR, MD
University of California, San Diego

NICHOLAS PETRAKIS, MD
University of California, San Francisco

JOHN M. PETERS, MD
University of Southern California

BRENDA SOLORZANO
CMA Staff
San Francisco

Alerts, Notices, and Case Reports

Mushroom Poisoning due to Amatoxin

Northern California, Winter 1996–1997

EILEEN G. YAMADA, MD, MPH
Sacramento, California
JANET MOHLE-BOETANI, MD
Berkeley, California
KENT R. OLSON, MD
San Francisco, California
S.B. WERNER, MD, MPH
Berkeley, California

OF MORE THAN 5,000 SPECIES of mushrooms in the United States, approximately 100 are poisonous, and less than a dozen are deadly.[1–3] More than 90% of deaths are attributable to *Amanita phalloides*, (*A. phalloides*) also referred to as the "death cap."[3–5] Ingestion of a single *A. phalloides* mushroom can be lethal.[2,6]

A. phalloides poisonings have increased in the United States and California.[7,8] In California during the winter of 1995–1996, 13 people were hospitalized after eating *A. phalloides*[8]; 10 poisonings due to *A. phalloides* occurred between 27 December 1996 and 5 January 1997 in Northern California; 2 patients died. Our investigation describes these 10 patients; we offer suggestions for clinicians and recommendations for preventing future cases.

Report of Cases

In early January 1997, the California Department of Health Services was notified by a liver transplant unit at a tertiary care hospital about an apparent cluster of mushroom poisonings. We sought additional cases by contacting local health departments and the California Poison Control System. A case-patient was defined as a person with vomiting and diarrhea beginning ≥6 hours after consuming wild mushrooms in California during December 1996 or January 1997.

In addition to reviewing the medical records of all 10 case-patients, we interviewed 7 of the 8 survivors directly and a relative of each of the 2 deceased patients.

(Yamada EG, Mohle-Boetani J, Olson KR, Werner SB. Mushroom poisoning due to amatoxin—Northern California, winter 1996–1997. West J Med 1998; 169:380–384)

From the Preventive Medicine Residency (Dr Yamada), the Chronic Disease Control Branch (Dr Yamada), and the Disease Investigations and Surveillance Branch (Drs Mohle-Boetani and Werner), California Department of Health Services, Sacramento and Berkeley, California; and the California Poison Control System (Dr Olson), University of California, San Francisco, California.

Reprint requests to Eileen G. Yamada, MD, MPH, California Department of Health Services, Chronic Disease Control Branch, PO Box 942732, MS-725, Sacramento, CA 94234-7320. E-mail: eyamada@dhs.ca.gov

We asked about prior illness after eating wild mushrooms and their awareness of the risk of wild mushroom poisoning. We queried case-patients where they collected mushrooms and their knowledge and prior experience in collecting mushrooms.

Results

Demographics and Clinical Information

Nine of the 10 case-patients were men; the median age was 23 years (range 12–68 years). Of 9 with race/ethnicity information, 6 were white/non-Hispanic, 2 were Filipino, and 1 was multiracial (white/African-American). Patients resided in Alameda, Mendocino, San Francisco, Santa Clara, and Sonoma counties in California.

The median interval from ingestion to the onset of gastrointestinal symptoms was 12 hours (range 8–26 hours). Reported symptoms included vomiting (100% of patients), diarrhea (100%), nausea (100%), abdominal cramping (60%), and weakness (70%). Nine patients were hospitalized for a median of 6 days (range 2–8 days); the two deaths occurred on the sixth and eighth hospital days. Serum transaminases peaked 2 to 4 days after mushroom consumption; the median peak aspartate aminotransferase (AST) was 3,284 U/liter (range 594–6,998 U/liter; normal range 0–35 U/liter), and the median peak alanine aminotransferase (ALT) was 4,660 U/liter (range 38–7,120 U/liter; normal range 0–35 U/liter).[9] For the eight patients with prothrombin time (PT) results, the median PT was 18.0 sec (range 12.7 to >60 sec, normal range 11–15 sec) (Table 1).[9]

Treatment included intravenous hydration (100% of patients), H_2-blockers (100%), activated charcoal (90%), penicillin (60%), and *N*-acetylcysteine (80%). Fresh frozen plasma and vitamin K were administered to 30% and 60% of patients, respectively. Six patients received repeated doses of activated charcoal. Five of the 9 hospitalized patients were transferred to a tertiary-care hospital; none had liver transplantation; 2 died before liver transplant could be arranged. The 2 fatal case-patients had multiorgan failure; both required hemodialysis, and 1 required ventilatory support. The two deaths occurred in patients with the highest PTs.

Knowledge and awareness of the dangers of mushroom collection and ingestion

Of the three mushroom collectors interviewed, all believed they could identify poisonous mushrooms. No mushrooms had been presented to and examined by an expert mycologist before ingestion. Two collectors incorrectly thought that poisonous mushrooms could be identified by color. One incorrectly thought the presence of a "cup" or volva at the base of the stem indicated that the mushroom was edible (a volva is actually a feature of

TABLE 1.—*Case-Patient Information, Mushroom Poisoning, California, 1996–1997*

Patient	Age	Sex	Outcome	Hospital Days	Peak AST (U/liter)	Peak ALT (U/liter)	Peak PT (sec)	Latency Period to Gastrointestinal Symptoms (hours)	Time to Medical Care (hours)	Time to Diagnosis (hours)
Group 1										
1	42	M	Recovery	6	3,284	6,000	32.1	12	16.5	16.5
2	17	M	Recovery	6	2,378	4,639	12.7	15	17.5	17.5
3	12	M	Recovery	6	2,162	4,808	31.7	16	17.5	17.5
Group 2										
4	18	M	Recovery	3	6,998	5,794	15.8	13	43	43
5	19	M	Recovery	2	594	930	NA	11	48	48
6	17	M	Recovery	0	19	38	NA	11	46	46
Group 3										
7	30	M	Recovery	4	2,392	3,062	18.0	12	25	25
8	28	F	Recovery	3	3,632	7,120	17.7	12	12–24	39
Group 4										
9	32	M	Death	8	4,276	4,313	60.0	8	21	21
Group 5										
10	68	M	Death	6	3,499	4,681	34.0	12	27	~120

Amanita species). Other erroneous methods mentioned by these collectors included the avoidance of bitter-tasting mushrooms and mushrooms with a milky discharge when cut.

Case-patients did not report illness after eating wild mushrooms in the past, yet they all knew that some mushrooms are poisonous. Only one had heard about mushroom poisoning from the media during the year before his mushroom poisoning. Three patients were unaware that they had actually eaten wild mushrooms, since the poisonous mushrooms were an ingredient in foods prepared by others. None of the interviewed patients planned to eat wild mushrooms in the future.

Case Circumstances

The first group was a Russian family; the parents collected wild mushrooms while hiking near Lake Chabot in the San Francisco Bay Area. This was the first time that the father had collected mushrooms in the United States after moving from Russia 2 years earlier. He collected mushrooms with impunity in Russia for approximately 30 years and thought that he knew the types of mushrooms that he was collecting. He had learned about collecting mushrooms from family members with years of mushroom collecting experience, from books and field guides, and from a botany class in a Russian middle school.

The mushrooms were fried and eaten by the father and his two sons, who became ill 12 to 16 hours after eating the mushrooms. All three ill family members were diagnosed at a local emergency department, transferred to a tertiary care facility, and discharged 6 days later (Table 1). Fragments of one variety of the leftover mushrooms were identified as *Boletus amygdalinus,* which is limited in toxicity to gastrointestinal symptoms.

In the second group, an 18-year-old white man collected mushrooms after hiking about 0.4 km (0.25 miles) from a road in rural Mendocino county. He had collected mushrooms 8 to 10 times previously and thought these mushrooms were "caesars." (He may have been referring to *A. caesarea*, an edible mushroom, which looks much like *A. phalloides*. Even experts may have a difficult time distinguishing the two.) He had learned about mushroom collecting from books, field guides, and a friend with more than 15 years of collecting experience.

The mushrooms were dried, prepared with deviled eggs, and served at a small New Year's Eve party. He and two friends ate the mushrooms at the party. The collector was evaluated in the emergency department of a local medical center and transferred to a tertiary-care facility. The two friends were then contacted by the local medical center for evaluation. One friend was hospitalized; the other was followed as an outpatient. The two hospitalized patients improved and were discharged after 2 to 3 days (Table 1). Leftover mushrooms were identified as *A. phalloides*.

In the third group, a 30-year-old Filipino man collected mushrooms after hiking about 1.2 km (0.75 miles) at a local regional park in Oakland. He had collected wild mushrooms twice in the previous 4 years but had not previously noticed this variety of mushroom. He learned about mushrooms by reading books and field guides. He prepared the mushrooms in a soup for himself and a girlfriend, became ill, and was hospitalized about 25 hours later. His girlfriend was initially diagnosed with ulcer/dyspepsia and prescribed cimetidine at a medical clinic. Because of her continued nausea, vomiting, and diarrhea, she sought medical care in an emergency department where the history of wild mushroom ingestion was obtained, and she was hospitalized approximately 39 hours after eating the wild mushrooms. Both patients improved and were discharged after 3 to 4 days (Table 1). No mushrooms were available for identification.

In the fourth "group," a 32-year-old white man collected mushrooms in his girlfriend's backyard. As a child, he learned about mushroom collecting from relatives who had collected mushrooms for many years in Italy. He sautéed the mushrooms in butter. He was diagnosed with mushroom poisoning in the emergency department of a community hospital, transferred to a tertiary care facility, and developed multiorgan failure. Nine days after eating the mushrooms, he died. Leftover mushrooms were identified as *A. phalloides* by a mycologist.

In the fifth "group," a 68-year-old man collected mushrooms on a golf course. He had collected mushrooms "hundreds of times" over "many" years in the Philippines, where he had learned about wild mushroom collecting from family members, but this was the first time he had collected them since moving to the United States 9 years previously. He cooked the mushrooms in a soup. He was admitted to a local hospital with an initial diagnosis of gastroenteritis. The history of mushroom ingestion was not elicited until 3 days after admission, and therefore, he never received activated charcoal. Seven days after ingestion, he died.

Discussion

Clinical symptoms and treatment

All 10 poisonings were likely due to ingestion of *A. phalloides*, an amatoxin-containing mushroom. All case-patients had a delayed onset of gastrointestinal symptoms (8–16 hours), which is typical for *A. phalloides*.[10] Mushroom poisonings with delayed onsets—6 hours or more after ingestion—tend to be life-threatening poisonings, while poisonings with onsets less than 2 hours after ingestion are rarely lethal.[2,11] Co-ingested mushrooms that cause symptoms soon after ingestion, however, may mask the asymptomatic period of a lethal mushroom ingestion.[2,5,7] The first group, the Russian family, probably ate more than one type of mushroom, since *Boletus amygdalinus* would not be expected to produce the hepatoxicity they experienced.

The case-patients in this series exhibited the characteristic progression of cellular damage recognized after ingestion of *A. phalloides*. After vomiting and diarrhea subside, patients clinically improve 24 to 48 hours after ingestion; however, the hepatotoxic and nephrotoxic effects then begin to manifest, as occurred in nine of the patients (Table 1).[5,7] Fulminant hepatic failure, encephalopathy, renal failure, hypofibrinogenemia and coagulopathy, acidosis, hypoglycemia, and gastrointestinal hemorrhage may occur.[7,12]

Fatalities have been correlated with young age (<10 years), short latency from ingestion to onset of gastrointestinal symptoms, and the severity of coagulopathy.[6,13] In our case series, the two patients with the highest PTs died; one of the deaths also occurred in the patient with the shortest latency period (Table 1). Twenty percent of the patients in our series died, consistent with published mortality rates of 9%–30%.[3,10,11,14,15] Multiorgan failure preceded the two deaths in our case series, but, in agreement with published reports, transaminase levels in the first few days did not directly correlate with death.[6,13,16]

The serious toxic effects of *A. phalloides* have been attributed to amanitins, cyclic octapeptides.[6] These amatoxins interrupt protein synthesis and cause cell death.[6,17–20] Because of their high rate of protein synthesis, gastrointestinal and liver cells are particularly susceptible to injury, causing the characteristic signs and symptoms of toxicity.[6,11,19,20] Amatoxins are readily absorbed from the intestine and are transported across the hepatocyte by bile transport carriers.[21] About 60% of the toxin undergoes enterohepatic circulation by biliary excretion,[18] and the circulating serum toxin is eliminated rapidly in the urine.[11,18,19] Thus, early hydration and interruption of the enterohepatic circulation are important in the treatment of *A. phalloides* poisoning.

To optimize care, early diagnosis is essential. Health care providers should always consider mushroom ingestion in the differential diagnosis of patients who present with gastrointestinal symptoms and remember that patients may not attribute their symptoms to wild mushrooms eaten 6 to 24 hours earlier. Mushroom particles should be evacuated from the stomach if the patient is seen within 1 hour of ingestion. Activated charcoal should be given immediately to bind any remaining toxin in the gastrointestinal tract. To interrupt the enterohepatic circulation of the toxin, repeated doses of activated charcoal should be administered; gastroduodenal drainage may also be beneficial. Early and aggressive intravenous fluids/electrolytes to correct and maintain adequate hydration and electrolyte balance are essential, and other supportive care should be given (such as fresh frozen plasma and vitamin K for coagulopathy). Other proposed, but unproven, treatments include high-dose penicillin G, silibinin, cimetidine, and *N*-acetylcysteine.[6,7,13] Although there have been no definitive controlled trials, silibinin and high-dose penicillin G appear to be the most promising.[6,7,11,15,19] Silibinin has not been approved for use in the United States.[6] Hemoperfusion, hemodialysis, and hemofiltration to eliminate amatoxin are of limited value.[19] Liver transplantation is indicated for fulminant hepatic failure. Patients with markedly prolonged PT that is only partially correctable and other findings such as acidosis, hypoglycemia, gastrointestinal hemorrhage, hypofibrinogenemia, and increased ammonia level after a significant increase in liver enzymes should be evaluated for urgent liver transplantation, ideally before progressing to advanced hepatic encephalopathy.[3,12] A liver transplant service and poison control center should be contacted early in the hospital course to guide treatment and to expeditiously identify liver transplant candidates (Table 2).

Seasonality and locations of A. phalloides

All cases described in this series occurred during the peak season for *A. phalloides*, the fall and winter months in California; *A. phalloides* has, however, been found throughout the year.[11] The public should be reminded frequently that eating wild mushrooms can be fatal, and

TABLE 2.—*Recommended Care of Suspected Cases of Poisoning due to A. Phalloides*

Obtain a full history including time of eating the mushrooms, time of onset of symptoms, and number of mushroom species eaten
Submit mushroom remnants to an expert mycologist for identification
Ask about others who may have ingested mushrooms so that they can be promptly evaluated
Immediately administer oral activated charcoal
Hydrate with intravenous fluids to correct dehydration and maintain adequate urine output for elimination of the toxin
Monitor and support all vital functions
Prevent toxin absorption by interrupting the enterohepatic circulation of the toxin with repeated doses of activated charcoal (duodenal drainage with a nasoduodenal tube may also be of benefit)
Manage fluid balance, electrolytes, and blood glucose
Monitor and manage complications due to impaired liver function, renal function, and coagulopathy
Call the local poison control center for further advice on clinical management
Liver transplantation: Call the liver transplant service early in the course of management so that the appropriate patients can be transferred to a tertiary care facility and liver donor candidates can be identified, if necessary
Call the local health department early to facilitate investigations and appropriate public health announcements and warnings

medical care providers should consider *A. phalloides* poisoning throughout the year, particularly during the fall and winter months in the West.

Distinguishing A. phalloides

None of the methods stated by the collectors is adequate to identify edible mushrooms. There is no single test that can be used to determine the edibility of wild mushrooms. As has been stated, "NO RULE IS THE ONLY RULE."[1]

Figure 1.—The classic annulus and volva of an *Amanita phalloides* mushroom. (Photo by Kent R. Olson, MD)

A. phalloides is distinguished by an annulus (or skirt-like ring) around the midportion of the stem, white gills under the cap that are not attached to the stem, and a volva (or cup) at the base of the stem (Fig. 1).[10] Although the cup is an important distinguishing feature, it is easily left behind in the soil if the mushroom is broken off at the stem. The color of *Amanita* species has been described as pure white to moderate olive, olive-gray, greenish yellow, or yellowish brown.[22–24] *A. phalloides* is known to have variable appearances at different times of the year and at different locations, depending on weather, soil, and age of the mushroom.[10,13] Although *A. phalloides* is the most important cause of amatoxin poisoning, other *Amanita* species and *Galerina*, *Lepiota*, *Conocybe*, and *Corinarius* species also contain amatoxin.[6,10] Thus, distinguishing amatoxin-containing mushrooms can be quite difficult. There are edible species of mushrooms that appear similar in appearance to *A. phalloides*; however, because of the difficulty in distinguishing such edible species from *A. phalloides*, any mushrooms that fit the above description should never be ingested.

Immigrants, even if very experienced in their countries of origin, may not be able to distinguish poisonous from edible mushrooms in the United States. Two of our case-patients collected mushrooms for the first time in the United States although they had had significant experience in their native countries.

As illustrated by our case series, knowledge of mushrooms gained from family members or field guides is not sufficient to distinguish *A. phalloides* from edible mushrooms. If wild mushrooms are to be eaten, each specimen should be examined by a competent mycologist; experts may be found at local mycological societies and at university mycology and botany departments. Some may be willing to examine wild mushrooms, but it is impractical to expect that they will provide this service. There is no effective way to render *A. phalloides*

TABLE 3.—*Recommendations for Public Announcements*

Collecting and eating wild mushrooms can be dangerous and even deadly
One of the most deadly mushrooms can be found near populated areas in California
This deadly mushroom has a variable appearance: field guides and simple tests or rules cannot reliably differentiate poisonous from edible mushroom species
Relying on knowledge of family members with many years of experience in mushroom collecting is not adequate to distinguish this deadly mushroom
If wild mushrooms must be eaten, each mushroom should be examined individually by a competent mycologist and deemed edible
If you become ill after ingesting wild mushrooms, seek early medical care, mention the ingestion of wild mushrooms, and bring mushroom remnants for identification

mushrooms safe. Cooking or drying does not detoxify amatoxin, and the mushroom does not have a distinct smell or taste.[3,5,7] Accordingly, the selection of wild mushrooms for consumption should be left to recognized experts.

Awareness of potential dangers of poisonous mushrooms

Despite the fact that all interviewed case-patients knew that poisonous mushrooms existed, seven consciously ate wild mushrooms. Prior media exposure about mushroom poisoning was limited; only one person reported hearing about the dangers of mushroom poisoning in the media that year. Just as there are annual warnings before Thanksgiving about cooking poultry properly, public health announcements to warn the public about the potentially lethal consequences of wild mushrooms should be a routine event when the rains begin every fall (Table 3).

Reporting

Mushroom poisoning is reportable as a foodborne disease in California, and regulations require reporting of suspected cases by the health care provider by fax, telephone, or mail within 1 working day to the local health department. If there are two or more cases or suspected cases from separate households, there is an immediate reporting requirement by telephone.[25] Reporting facilitates public health follow-up, including announcements to the public.

Acknowledgments

We wish to thank the patients, family members, local hospitals, health care providers, the San Francisco Department of Public Health, Mendocino County Department of Public Health, and Santa Clara County Public Health Department for their assistance in obtaining clinical and historical information. We also thank Richard Kreutzer, MD, Julie Von Behren, MPH, and William Freedman, MD, for reviewing the questionnaire and Neal D. Kohatsu, MD, MPH, for reviewing the manuscript.

REFERENCES

1. Lincoff G, Mitchel DH. Toxic and Hallucinogenic Mushroom Poisoning. New York, Van Nostrand Reinhold Company, 1977

2. Blackman JR. Clinical approach to toxic mushroom ingestion. J Am Board Fam Pract 1994; 7:31–37

3. Pinson CW, Bradley AL. A primer for clinicians on mushroom poisoning in the West. West J Med 1996; 165:318–319

4. Barbato MP. Poisoning from accidental ingestion of mushrooms. Med J Aust 1993; 158:842–847

5. Becker CE, Tong TG, Boerner U, et al. Diagnosis and treatment of *Amanita phalloides*-type mushroom poisoning: use of thioctic acid. West J Med 1976; 125:100–109

6. Benjamin D. Mushrooms: Poisons and Panaceas. New York, W.H. Freeman and Company, 1995

7. Klein AS, Hart J, Brems JJ, Goldstein L, Lewin K, Busuttil RW. *Amanita* poisoning: treatment and the role of liver transplantation. Am J Med 1989; 86:187–193

8. Zevin S, Dempsey D, Olson K. *Amanita phalloides* mushroom poisoning—Northern California, January 1997. MMWR 1997; 46:489–492

9. Nicholl D. Appendix: therapeutic drug monitoring and laboratory reference ranges. In Tierney L, McPhee S, Papadakis M (Eds): Current Medical Diagnosis and Treatment. Stamford, CT, Appleton & Lange, 1996, pp 1439–1446

10. Olson KR, Pond SM, Seward J, Healey K, Woo OF, Becker CE. *Amanita phalloides*-type mushroom poisoning. West J Med 1982; 137:282–289

11. Jacobs J, VonBehren J, Kreutzer R. Serious mushroom poisonings in California requiring hospital admission, 1990–1994. West J Med 1996; 165:283–288

12. Pinson CW, Daya MR, Benner KG, et al. Liver transplantation for severe *Amanita phalloides* mushroom poisoning. Am J Surg 1990; 159:493–499

13. O'Brien BL, Khuu L. A fatal Sunday brunch: *Amanita* mushroom poisoning in a Gulf Coast family. Am J Gastroenterol 1996; 91:581–583

14. Pond SM, Olson KR, Woo OF, et al. Amatoxin poisoning in Northern California, 1982–1983. West J Med 1986; 145:204–209

15. Floersheim GL. Treatment of human amatoxin mushroom poisoning: myths and advances in therapy. Med Toxicol 1987; 2:1–9

16. Koppel C. Clinical symptomatology and management of mushroom poisoning. Toxicon 1993; 31:1513–1540

17. Lindell TJ, Weinberg F, Morris PW, Roeder RG, Rutter WJ. Specific inhibition of nuclear RNA polymerase II by alpha-amanitin. Science 1970; 170:447–449

18. Faulstich H. New aspects of Amanita poisoning. Klin Wochenschr 1979; 57:1143–1152

19. Serne EH, Toorians AWFT, Gietema JA, Bronsveld W, Haagsma EB, Mulder POM. *Amanita phalloides*, a potentially lethal mushroom: its clinical presentation and therapeutic options. Neth J Med 1996; 49:19–23

20. Weiland T. The toxic peptides from Amanita mushrooms. Int J Peptide Protein Res 1983; 22:257–276

21. Kroncke KD, Fricker G, Meier PF, Gerok W, Wieland T, Kurz G. Alpha-amanitin uptake into hepatocytes. J Biol Chem 1986; 261:12563–12567

22. Smith A, Smith H, Weber N. How to Know the Gilled Mushrooms. Dubuque, IA, William C. Brown Company Publishers, 1979

23. Smith A, Weber N. The Mushroom Hunter's Field Guide. The University of Michigan Press, 1980

24. McKnight K, McKnight V. A Field Guide to Mushrooms: North America. Boston, Houghton Mifflin Company, 1987

25. Title 17, California Code of Regulations, Section 2500: Reportable Diseases and Conditions

Thrombophilia in Ischemic Stroke

ANIL POTTI, MD
KHALED M. RABADI, MD
DARIN D. WILLARDSEN, MD
Fargo, North Dakota

CEREBROVASCULAR ACCIDENTS, WHICH are sometimes fatal, have a great impact on public health.[1] In young individuals, identification and modification of risk factors for cerebrovascular events can prevent recurrence and reduce further disability. Although hypercoagulable states are increasingly being reported as dominant risk factors, thrombophilia as a cause of ischemic stroke remains underdiagnosed. The possibility of multiple prothrombotic factors for thrombosis in an individual with recurrent strokes at atypical sites is rarely considered. We present a unique patient in whom, by sequential testing, a complete risk factor profile was identified.

Report of a Case

A 45-year-old man presented with acute right hemiparesis, dysarthria, and diplopia. Ten months earlier, he had presented with hemianesthesia and was diagnosed to have a thalamic infarct. At that time, essential thrombocythemia was diagnosed based on a markedly elevated platelet count of $1.11 \times 10^6/mm^3$, a bone marrow examination, and *in vitro* culture of hematopoietic progenitor cells. Treatment with hydroxyurea was begun.

During the episode we recount here, magnetic resonance imaging revealed left temporal, left thalamic, and bilateral cerebellar infarction. The patient had no history of illicit drug use, hypertension, rheumatic heart disease, atrial fibrillation, or diabetes. Family history was noncontributory. There was no clinical evidence of venous thrombosis. Initial laboratory work-up revealed normal hemogram, platelet count, lipid profile, fibrinogen level, erythrocyte sedimentation rate, and renal and hepatic function. Serum protein electrophoresis to evaluate the patient for possible macroglobulinemia was unrevealing. Peripheral blood smear showed macrocytosis and hypersegmented neutrophils. Red cell folate level was low, and serum vitamin B_{12} level was normal. A four-vessel cranial arteriogram and bilateral renal arteriogram to look for structural abnormalities and possible evidence of vasculitis demonstrated no major abnormalities. Transesophageal echocardiography showed no evidence of a patent foramen ovale or a possible source of cardiogenic embolus.

A magnetic resonance angiogram of the brain showed a thrombus at the bifurcation of the basilar artery. The consulting neurologist hypothesized that fragmentation of the thrombus "at the tip of the basilar artery" could account for the anatomical distribution of this patient's cerebral infarcts. Given the age of the patient, the normal platelet count during the current admission, and the results of angiography and the other imaging studies, a work-up for hypercoagulability was initiated (Table 1).

(Potti A, Rabadi KM, Willardsen DD. Thrombophilia in ischemic stroke. West J Med 1998; 169:385–386)

From the Department of Internal Medicine, MeritCare Medical Center, University of North Dakota School of Medicine and Health Sciences, Fargo, North Dakota
Reprint requests to Anil Potti, MD, Department of Medicine, 902 Oak St N, #16, Fargo, ND 58102. E-mail: anilpotti@meritcare.com.

TABLE 1.—*Results of diagnostic studies for hypercoagulability at 2 weeks and 6 months after the acute event*

	2 weeks	*6 months*	*Normal reference values*
Serum fibrinogen (g/liter)	2.7	2.5	2–4
Prothrombin time (sec)	12.6	12.4	10–13
Partial thromboplastin time (sec)	30.3	32.1	24–34.5
Plasma homocysteine (μmol/liter)	49	16	4–17
Functional protein C (%)	38	36	70–130
Functional antithrombin III (%)	97	102	80–120
Protein S (%)			
Total	81	80	50–120
Free	76	76	50–120
Hexagonal lupus anticoagulant (sec)	0.0	0.2	0–10
Cardiolipin IgG antibody	Negative	Negative	Negative
Cardiolipin IgM antibody	Negative	Negative	Negative
Serum viscosity	1.6	1.4	1.4–1.8
Red cell folate (ng/ml)	90	164	150–450
Serum vitamin B_{12} (pg/ml)	364	380	220–1000
Activated protein C resistance	Negative	Negative	Negative
Platelet count ($/mm^3$)	3.3×10^5	2.65×10^5	$1.5–4 \times 10^5$

The patient was not receiving anticoagulants.

The patient was found to have three hypercoagulable states: essential thrombocythemia, protein C deficiency, and hyperhomocysteinemia. Hyperhomocysteinemia might have been attributable to possible nutritional folate deficiency. The patient's neurologic deficit improved with physiotherapy. At discharge, the patient was maintained on low-molecular-weight heparin, vitamin B_{12}, folic acid, and pyridoxine supplements in addition to hydroxyurea.[2]

Six months later, the patient was asymptomatic and had minimal residual neurological deficit. The hypercoagulability work-up was repeated, confirming the presence of protein C deficiency, but the homocysteine level had decreased to the normal range (Table 1), presumably because the folate deficiency had been corrected (red cell folate level was normal after 6 months of supplements). Heparin cofactor II level, plasminogen activator level, and individual factor assays 6 months after the acute event were normal.

Discussion

Hypercoagulable states are underrecognized causes of ischemic stroke, and "dual" hypercoagulability as a cause of ischemic stroke is extremely rare.[3] To the best of our knowledge, coexistent protein C deficiency, hyperhomocysteinemia, and essential thrombocythemia has not been reported previously. It is important to realize, however, that various combinations of inherited or acquired hypercoagulable states exist and will be increasingly recognized.

Recent reviews on thrombophilia have discussed the concept of gene–gene interactions and gene–environment interactions in the genesis of mixed hypercoagulable states.[4] The possibility of synergism of risk factors in multiple coexistent prothrombotic states has also been noted.[4] Hence it is imperative that a complete evaluation for hypercoagulability be done at initial presentation in previously asymptomatic young individuals (with no known risk factors) presenting with acute cerebrovascular ischemic events.[5] This case emphasizes the fact that hyperhomocysteinemia is a modifiable risk factor that can be treated easily with pyridoxine or folate and vitamin B_{12} supplements. Our case also exemplifies the recent concept that ischemic stroke can be the first manifestation of essential thrombocythemia.[6] Although myeloproliferative disorders may be associated with protein C deficiency as a part of the syndrome complex, essential thrombocythemia, even when appropriately treated with hydroxyurea therapy, may lead to acquired protein C deficiency.[7,8] This consideration tends to support the therapeutic use of analgrelide (recently approved by the US Food and Drug Administration) in essential thrombocythemia. It was also interesting to note that contrary to expectation, our patient did not have factor V resistance to activated protein C, and had normal levels of plasminogen activator inhibitor-1 and antithrombin III.[7,9]

Acknowledgment

The authors are grateful to Dr. Martin F. Heyworth for helpful discussions and for reviewing the manuscript.

REFERENCES

1. Sacco RL. Risk factors and outcomes of ischemic stroke. Neurology 1995; 45:S10–S14

2. Cortelazzo S, Finazzi G, Ruggeri M, Vestri O, Galli M, Rodeghiero F, Barbui T. Hydroxyurea for patients with essential thrombocythemia and high risk of thrombosis. N Engl J Med 1995; 333:1132–1136

3. Hart RG, Kanter MC. Hematologic disorders and ischemic stroke. Stroke 1990; 21:1111–1121

4. Rosendaal FR. Risk factors for venous thrombosis: prevalence, risk and interaction. Semin Hematol 1997; 34:171–187

5. Landi G, D'Angelo A, Boccardi E, et al. Hypercoagulability in acute stroke: prognostic significance. Neurology 1988; 37:1667–1671

6. Arboix A, Besses C, Acin P, Massons JB, Florensa L. Ischemic stroke as first manifestation of essential thrombocythemia. Stroke 1995; 26:1463–1466

7. Bucalossi A, Marotta G, Bigazzi C, et al. Reduction of antithrombin III, protein C and protein S levels and activated protein C resistance in polycythemia vera and essential thrombocythemia patients with thrombosis. Am J Hematol 1996; 52:14–20

8. Cancelas JA, Garcia-Avello A, Garcia-Frade LJ. High plasma levels of plasminogen activator inhibitor-1 in polycythemia vera and essential thrombocythemia are associated with thrombosis. Thrombosis Res 1994; 75:513–520

9. Wieczorek I, MacGregor IR, Ludlam CA. Low protein C and S and activation of fibrinolysis in treated essential thrombocythemia. Am J Hematol 1995; 49:277–281

Acquired Sulfhemoglobinemia

An Underreported Diagnosis?

MUSTAFA NOOR, MD
ERNEST BEUTLER, MD
La Jolla, California

SULFHEMOGLOBINEMIA IS A disorder of hemoglobin characterized by cyanosis in the absence of cardiopulmonary pathology. Cyanosis is intense and becomes clinically apparent even at very low concentrations of sulfhemoglobin (SHb). A mean capillary concentration of only 0.5 g/dl SHb is sufficient for detectable cyanosis. This level is about 10 times less than the detectable level with deoxygenated hemoglobin.[1] SHb shares a similar peak spectral absorbance with methemoglobin (MetHb) at approximately 626 nm. Therefore, automated blood gas analysis using spectrophotometers does not accurately differentiate between MetHb and SHb. The clinical picture can be further confusing because many agents known to cause methemoglobinemia also have been reported to cause sulfhemoglobinemia. In most patients, sulfhemoglobinemia, unlike methemoglobinemia, has few adverse clinical consequences and will resolve spontaneously with the physiologic turnover of red blood cells. The clinician that may erroneously treat sulfhemoglobinemia as methemoglobinemia under the false impression from automated blood

(Noor M, Beutler E. Acquired sulfhemoglobinemia—an underreported diagnosis? West J Med 1998; 169:386–389)

From the Division of Graduate Medical Education and General Internal Medicine (Dr Noor) and the Department of Molecular and Experimental Medicine (Dr Beutler), Scripps Clinic and the Scripps Research Institute, La Jolla, California

Reprint requests to Ernest Beutler, MD, Department of Molecular and Experimental Medicine, 10550 North Torrey Pines Rd, La Jolla, CA 92037.

ABBREVIATIONS USED IN TEXT

Hb = hemoglobin
MetHb = methemoglobin
Shb = sulfhemoglobin

gas analyzers could potentially harm the patient. We report a case of drug-induced sulfhemoglobinemia initially misdiagnosed as methemoglobinemia based on blood gas analysis.

Report of a Case

A 69-year-old woman was admitted to the hospital with severe cyanosis. Approximately 1 week before admission, she had an uncomplicated lower urinary tract infection. She was initially treated with a regimen of 400 mg norfloxacin twice a day for 3 days. When symptoms persisted, the regimen was changed to trimethoprim/sulfamethoxazole (TMP/SMX), and 100 mg phenazopridine three times a day was added for urinary analgesia. Two days before admission, she noted "bluish stains on finger tips" that "would not wash away." On the day of admission, she was exercising on a treadmill when she noted onset of anterior chest tightness lasting 3 minutes followed by dizziness and marked exertional intolerance. At initial outpatient evaluation, she was noted to have severe acral cyanosis but did not appear to be in respiratory distress. An electrocardiogram showed no acute ischemia, and she was transferred for admission.

Her medical history included hypertension, hypercholesterolemia, and fibromyalgia. She also suffered from irritable bowel syndrome with chronic constipation. Besides TMP/SMX and phenazopridine, her medications included simvastatin, lisinopril, trazodone, estrogen, and progesterone.

On examination she was alert and in no acute respiratory distress. Her blood pressure was 138/70 mmHg, pulse 70, respiratory rate 20, and temperature 36.5°C. A slate-gray color to her skin with accentuation at fingers and toes was noted. Mucous membranes had a violaceous hue with dark conjunctival vessels. Cardiorespiratory examination was normal. Extremities were warm and well perfused.

Pulse oximetry on room air revealed a hemoglobin oxygen saturation of 78%, which improved to only 80% with 100% O_2 delivered by face mask. Arterial blood gas analysis on 100% oxygen was performed using a cooximeter (Model IL482, Instrumentation Laboratory, Lexington, Massachusetts) and revealed a pH of 7.43, partial pressure of oxygen 337 mmHg, partial pressure of carbon dioxide 32 mmHg, and Hb oxygen saturation 82%. The MetHb level was 24%. Hb level was 11.3 g/dl and hematocrit 33.6%; all indices were normal. The white cell count was 6500/mm^3 with a normal differential. Electrolytes were normal. Blood urea nitrogen was 20 mg/dl and creatinine 1.5 mg/dl. CK was 88 U/liter and lactate dehydrogenase 166 U/liter.

An initial diagnosis of toxic methemoglobinemia was made. TMP/SMX and phenazopyridine were stopped and vitamin C was added to the patient's regimen. She was given two doses of methylene blue at 2 mg/kg, which failed to resolve cyanosis. Further studies revealed that Hb electrophoresis was normal, with 97.1% HbA and 2.9% HbA_2. Erythrocyte glutathione level was 6.9 mmol/g Hb (normal range 4.5–8.7 mmol/g Hb). MetHb level by spectrophotometric assay was 0.7 g/dl (normal <1.5 g/dl) and SHb 0.754 g/dl (normal <0.037 g/dl). Her hospital course was uncomplicated and gradual spontaneous resolution of cyanosis was noted. SHb level over the next 3 weeks revealed a gradual decline at the rate of the normal physiologic turnover of the red blood cells (Figure 1).

Discussion

Although uncommon, SHb and MetHb are important causes of cyanosis. They must be differentiated early to avoid possible harm to the patient with the treatment rendered. Sulfhemoglobin derives its name from the fact that it can be produced *in vitro* from the action of hydrogen sulfide on hemoglobin. The histidine imidazole group of the porphyrin ring is protonated at the sixth position with sulfur atom attached to the β carbon on the porphyrin ring. The incorporation of the sulfur into hemoglobin results in oxidative denaturation of the molecule. This severe disturbance of tertiary protein structures explains the considerable departure of the absorption spectrum of SHb from that of Hb. The final product of this reaction is an irreversible hemichrome that cannot be reconverted to normal hemoglobin.

The sulfamethoxazole molecule contains a sulfanilimide group, SO_2NH_2, that can react with ferryl hemoglobin ($HbFe^{4+}$) in the presence of hydrogen peroxide (H_2O_2). Sulfonamides, the class of antibiotics to which sulfamethoxazole belongs, were developed from aniline dye as the earliest antibacterial agents.[2] The anilines are well known to cause sulfhemoglobinemia and methemoglobinemia.[3,4] Other concurrent physiologic factors might enhance this reaction. There have been reports that chronic constipation may predispose to SHb formation. Theoretically, the increased colonic transit time leads to increased bacterial breakdown of amino acids with resultant release of hydrogen sulfide.[5]

Dyspnea and other signs of end organ damage are uncommon in sulfhemoglobinemia because cyanosis becomes clinically apparent at extremely low concentrations. A SHb concentration of only 0.5 g/dl is sufficient to cause severe cyanosis; this concentration is 10 times less than that of deoxyhemoglobin needed to cause clinically detectable cyanosis. In addition, the apparent oxygen delivery to the tissue is actually facilitated by the changes in hemoglobin conformation.[6] At low levels of abnormal pigment, only one or two of the hemoglobin tetramers are sulfurated. The unsulfurated tetramers shift toward the unliganded conformation, which in turn reduces the oxygen affinity of their unmodified subunits.

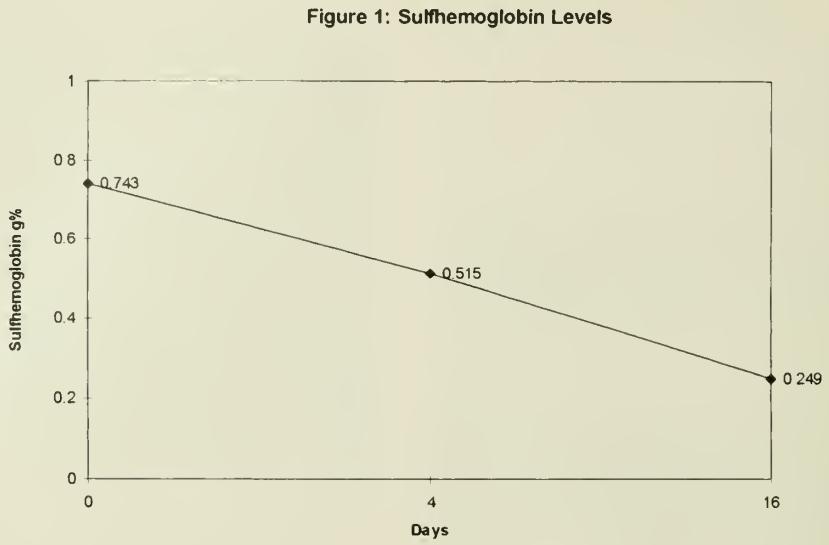


Figure 1.—Sulfhemoglobin levels during the patient's medical course.

This shift to the right of the oxygen dissociation curve actually ameliorates the effects of the reduced oxygen binding capacity and facilitates oxygen delivery to the tissue. Dyspnea is uncommon unless the level of SHb is extremely high. In the majority of patients, despite intense cyanosis, little more than careful clinical observation is needed. The abnormal hemoglobin disappears with the physiologic turnover of red blood cells.

Methemoglobin, on the other hand, is an oxidation product of hemoglobin. The resultant ferric hemoglobin ($HbFe^{3+}$) cannot reversibly bind oxygen. In the physiologic state, hemoglobin is oxidized at a very slow rate to MetHb. This steady state is maintained by the cell's endogenous mechanisms, which can transfer an electron back to the heme moiety, thereby regenerating reduced ferrous hemoglobin ($HbFe^{2+}$).[7] There are several known cellular mechanisms for preventing oxidation of hemoglobin. These include glutathione peroxidase, cytochrome b5 reductase, and catalase.[8] Damage will occur to red blood cells if an abnormally increased oxidant stress exceeds the normal source of reducing power; if there is a deficiency of reducing power; or if there are structural abnormalities of the hemoglobin that will render it more susceptible to the oxidative stresses. In the oxidized ferric state, the hemoglobin molecule itself also undergoes conformational changes that increase the oxygen affinity of the remaining three ferrous heme groups. The loss of oxygen-carrying capacity is thus further augmented, and this combination of effects may present a serious medical emergency when the MetHb levels rise to comprise 25% or more of the total pigment.

Clinically acute toxic methemoglobinemia is treated by administration of methylene blue. The NADPH formed in hexose monophosphate pathway can rapidly reduce MetHb to hemoglobin.[9] The onset of action is very rapid, with immediate resolution of cyanosis. The regeneration of NADPH requires an intact pentose phosphate pathway. If administered to those patients who are glucose-6-phosphate dehydrogenase (G6PD) deficient, methylene blue has no effect and can induce acute hemolysis.[10] Hemolysis has also been reported after administration of repeated doses of methylene blue even in those patients with normal G6PD.[11] The clinical consequences of such adverse reactions are serious and can include dyspnea, precordial pain, restlessness, apprehension, and persisting cyanosis.

The error in this case arose from reliance on blood gas values obtained using automated blood gas analyzers. The automated blood gas analyzers such as the IL482 Co-Oximeter System are equipped with a program for calculating total hemoglobin, percent oxyhemoglobin, percent carboxyhemoglobin, percent methemoglobin, and percent reduced hemoglobin. An anticoagulated whole blood sample is aspirated into the instrument, mixed with diluent, hemolyzed, and brought to a constant temperature in the cuvette. Monochromatic light at four specific wavelengths (535, 582.2, 594.5, and 626.6 nm) passes through the cuvette to a photodetector, which measures the absorbance and computes the percentages of different forms of hemoglobin.[12] The presence of other abnormal forms of hemoglobin with a different spectral absorbance can introduce errors in this measurement. These include presence of SHb, high MetHb levels, interfering dyes such as indocyanine, lipemic samples, and high bilirubin levels. These species can significantly absorb light at these wavelengths and introduce errors in the results. Of note, SHb has a peak spectral absorbance similar to that of MetHb, explaining a limitation of the system. The presence of this type of hemoglobin with an oxygen affinity different from that of oxygenated Hb is a rare but important source of error.[13] The presence of SHb has also been found to be an established source of error in the spectrophotometric determination of carboxy Hb.[14] In the case reported here, presence of SHb with a similar

set of maximum absorptive spectrum at 626 nm was erroneously calculated by the cooximeter as MetHb. The correct diagnosis was made from the results of an assay based on the difference in absorbance between MetHb and cyanomethemoglobin.[15,16] With the addition of cyanide, methemoglobin forms cyanomethemoglobin, thus losing its peak absorbance at 626 nm. Sulfhemoglobin, on the other hand, is an irreversible hemichrome, and unaffected by the cyanide, it retains its peak absorbance at 626 nm.

Conclusion

Sulfhemoglobinemia is a relatively benign clinical presentation of hemoglobin pigment. The diagnosis is frequently missed because automated spectrophotometers generally report this abnormal form of hemoglobin (with the peak absorbance at 626 nm) as MetHb, not differentiating it from SHb. When faced with cases of acute toxic methemoglobinemia as reported by blood gas analysis, the clinician should be aware of this error, since treatment can have potential for adverse outcomes. In the future it would be of interest to know the prevalence of such errors reported in routine blood gas analysis using automated blood gas analyzers.

REFERENCES

1. Finch CA. Methemoglobinemia and sulfhemoglobinemia. N Engl J Med 1948; 239:470–478

2. Goodman L, Gilman A. The Pharmacologic Basis of Medical Therapeutics, 8th ed. New York, McGraw Hill, 1990, p 1047

3. Bass AD, Saulter WT. 2-Anilinoethanol—an industrial hazard. JAMA 1943; 123:761–763

4. Reynold TB, Ware AG. Sulfhemoglobinemia following habitual use of acetanilide. JAMA 1952; 149:1538–1541

5. Discombe G. Sulfhaemoglobinaemia and glutathione. Lancet 1960; ii:371–372

6. Park CM, Nagel RL. Sulfhemoglobinemia: clinical and molecular aspects. N Engl J Med 1984; 310:1579–1584

7. Cox WW, Wendel WB. Normal rate of reduction of net hemoglobin in dogs. J Biol Chem 1942; 143:331–340

8. Hultquist DE. Methemoglobin reduction system for erythrocytes. In Fleischer S, Packer L (Eds): Methods in Enzymology, vol. 52. New York, Academic Press, 1978

9. Goluboff N, Wheaton R. Methylene blue-induced cyanosis and acute hemolytic anemia complicating the treatment of methemoglobinemia. J Pediatr 1961; 58:86–89

10. Rosen PJ, Johnson C, McGehee WG, Beutler E. Failure of methylene blue treatment in toxic methemoglobinemia. Association with glucose-6-phosphate dehydrogenase deficiency. Ann Intern Med 1971; 75:83–86

11. Harvey JW, Keitt AS. Studies of the efficacy and potential hazards of methylene blue therapy in aniline-induced methaemoglobinaemia. Br J Haematol 1983; 54:29–41

12. IL482 Co-Oximeter System. Operator's manual, section 1.3. Lexington, Massachusetts, Instrumentation Laboratory

13. Zwart A, Buursma A, van Kampen EJ, Oeseburg B, van der Ploeg PH, Zijlstra WG. A multi-wavelength spectrophotometric method for the simultaneous determination of five haemoglobin derivatives. J Clin Chem Clin Biochem 1981; 19:457–463

14. van Kampen EJ, Volger H, Zijlstra WG, et al. Spectrophotometric determination of carboxyhemoglobin in human blood and the application of this method to the estimation of carbonmonoxide in gas mixtures. Klonikl Ned Akad Wetenschap Proc 1951; 57:320–331

15. Dijkhuzen P, Buursma A, Gerding AM, Zijlstra WG. Sulfhaemoglobin. Absorption spectrum, millimolar extinction coefficient at lambda = 620 nm, and interference with the determination of hemoglobin and of haemoglobin-cyanide. Clin Chim Acta 1977; 78:479–487

16. Beutler E. Carboxyhemoglobin, methemoglobin, and sulfhemoglobin determinations. In Beutler E, Lichtman MA, Coller BS, Kipps TJ (Eds): Hematology. New York, McGraw Hill, 1995, pp L50–L51

Commentary

Shuffling Off This Mortal Coil

A Shakespearean Perspective on Death and Dying

HOBART W. WALLING, MA, *St. Louis, Missouri*

Death remains life's greatest mystery, and our efforts to understand it may be a defining quality of humanity. Surprisingly, this ubiquitous experience has been largely underresearched. A Medline subject search of the core clinical literature (*Abridged Index Medicus*) identifies only 138 articles (mostly essays and editorials) published from January 1995 to November 1998 on attitudes toward death and only 4 articles on thanatology (the study of the theory, doctrine, and philosophy of death). In contrast, a similar search reveals more than 3,900 articles concerning the polymerase chain reaction, an esoteric laboratory technique.

Although this is admittedly a somewhat stilted comparison, perhaps this relative paucity of information stems from an avoidance of death in the traditional medical model, whose currency is the prolongation of life. Certainly, "[w]hat is not acknowledged can hardly be dealt with successfully."[1(p1232)] In our culture, death is not accepted as a natural part of life, but is "the enemy, to be battled up to the last minute,"[2(p234)] and this mentality is reflected by trends in medical research and education. Several recent articles address the pragmatic elements of care for the dying,[1,3] while fewer discuss the emotional and compassionate aspects of decision-making and care in the late twilight of life.[4,5] This lack is unfortunate, as physicians often play unique roles at the interface between life and death and should be comfortable discussing death with patients and their families.

Although underappreciated in medical journals, the topic of death is addressed abundantly in classical literature, which offers a special approach to grasping life's final voyage. If art indeed imitates nature, then the writings of William Shakespeare (1564–1616), which express ideas of lasting interest, may be archetypal for the human experience. This essay explores Shakespeare's work to help clinicians consider anew our interactions with patients and their mortality, with the goals of heightening compassion and enhancing the quality of care.

I have previously presented a discussion of Kübler-Ross's five stages of dying (denial, anger, bargaining, depression, and acceptance) in the works of Shakespeare.[6] Shakespearean study suggests additional themes concerning our reactions to death: fear, uncertainty, powerlessness, regret, loneliness, and concern for the loss of dignity and autonomy. Suicide, "appropriate" death, and bereavement are also discussed.

Fear

Distressing factors during endstage illness can be both physical and physiological (fear of pain, suffering, and disfigurement) as well as psychosocial (fear of dependency, abandonment, isolation, and loss of control). Understanding these fears may allow us to offer assistance and reassurance and to reaffirm our involvement with the patient throughout the course of illness.[7]

Fear of death is a powerful Shakespearean theme. "The sense of death is most in apprehension, / And the poor beetle, that we tread upon, / In corporeal sufferance finds a pang as great / As when a giant dies.... The weariest and most loathed worldly life, / That age, ache, penury, and imprisonment / Can lay on nature, is a paradise / To what we fear of death" (*Measure for Measure* III:i, 76–79, 126–129).

Fear of the unknown contributes to Hamlet's hesitation to avenge his father's murder at the hands of his uncle, Claudius. Although Hamlet vows to sweep to his revenge "with wings as swift / As meditation, or the thoughts of love" (*Hamlet, Prince of Denmark* I:v, 29–30), he becomes grounded in melancholy pessimism and self-recrimination. In the soliloquy below, a fear of the unknown dissuades him from taking his own life.

> To be, or not to be, that is the question:—
> Whether 't is nobler in the mind, to suffer
> The slings and arrows of outrageous fortune;
> Or to take arms against a sea of troubles,
> And by opposing end them?—To die—to sleep,
> No more;—and, by a sleep, to say we end

(Walling HW. Shuffling off this mortal coil—a Shakespearean perspective on death and dying. West J Med 1998; 169:390–395)

From the Department of Pharmacological and Physiological Science, Saint Louis University Health Sciences Center, St. Louis, Missouri.

Shakespeare citations from *The Illustrated Stratford Shakespeare*, London, Chancellor Press, 1982.

Reprint requests to H.W. Walling, Department of Pharmacological and Physiological Science, Saint Louis University Health Sciences Center, St. Louis, MO 63104. E-mail: walling@slu.edu

The heart-ache, and the thousand natural shocks
That flesh is heir to,—'t is a consummation
Devoutly to be wish'd. To die,—to sleep:—
To sleep! perchance to dream:—ay, there's the rub,
For in that sleep of death what dreams may come,
When we have shuffled off this mortal coil,
Must give us pause. There's the respect,
That makes calamity of so long life:
For who would bear the whips and scorns of time,
The oppressor's wrong, the proud man's contumely,
The pangs of despis'd love, the law's delay,
The insolence of office, and the spurns
That patient merit of the unworthy takes,
When he himself might his quietus make
With a bare bodkin? who would these fardels bear,
To grunt and sweat under a weary life,
But that the dread of something after death,—
The undiscover'd country, from whose bourn
No traveller returns,—puzzles the will,
And makes us rather bear those ills we have
Than fly to others that we know not of?

(*Hamlet* III:i, 56–82)

For Hamlet, the fear of a formless unknown is a sufficient inducement to endure the (surprisingly modern) burdens of life. Milton expands on this theme: "To be no more; sad cure; for who would lose, / Though full of pain, this intellectual being, / Those thoughts that wander through Eternity, / To perish rather, swallow'd up and lost / In the wide womb of uncreated night, / Devoid of sense and motion?"[8]

Other characters connect specific images with their fear of death. Richard III declares in recalling a horrific dream, "What sights of ugly death within mine eyes! / Methought I saw a thousand fearful wracks; / A thousand men that fishes gnaw'd upon; / ...Unto the kingdom of perpetual night" (*Richard III* I:iv, 21–25, 47). The association of death with terrestrial imagery again suggests an inability to grasp the infinite.

Uncertainty

Some individuals acknowledge an uncertainty for what befalls the soul after death without expressing fearfulness. When Brutus declares "O, that a man might know / The end of this day's business, ere it come!" (*Julius Caesar* V:i, 123–124), the reader appreciates a sense of curiosity rather than apprehension. The following example is more pensive and also echoes Hamlet.

Ay, but to die, and go we know not where;
To lie in cold obstruction and to rot;
This sensible warm motion to become
A kneaded clod; and the delighted spirit
To bathe in fiery floods, or to reside
In thrilling regions of thick-ribbed ice;
To be imprison'd in the viewless winds,
And blown with restless violence round about
The pendant world;

(*Measure for Measure* III:i, 115–123)

Othello approaches this theme from yet another angle as he contemplates action against his wife, Desdemona, whom he mistakenly suspects (through the duplicity of his ensign Iago) of infidelity:

Yet she must die,...
...but once put out thy light,
Thou cunning'st pattern of excelling nature,
I know not where is that Promethean heat
That can thy light relume. When I have pluck'd thy rose,
I cannot give it vital growth again,
It needs must wither:

(*Othello* V:ii, 6, 10–15)

Othello's thoughts center on the permanence of death and the attendant loss of life's dynamic beauty. Although awed by the life force, he expresses no obligation to protect it. Discovering Iago's deception too late, "perplex'd in the extreme," Othello "lov'd not wisely, but too well" (V:ii 348, 346).

Powerlessness

Death's inevitability may engender feelings of powerlessness; alternatively, it may offer a sense of peace through resignation. A popular notion in Shakespeare's age (and even today) is that lives were predestined and controlled by arbitrary higher powers, that "the stars above us, govern our conditions" (*King Lear* IV:iii 33). For example, Romeo portends with deterministic calm that he will die in a fashion beyond his control.

I fear, too early; for my mind misgives,
Some consequence, yet hanging in the stars,
Shall bitterly begin his fearful date
With this night's revels; and expire the term
Of a despised life, clos'd in my breast,
By some vile forfeit of untimely death:
But He, that hath the steerage of my course,
Direct my sail.

(*Romeo and Juliet* I:iv, 106–113)

Some may take comfort that death is a part of the cycle of life. Juliet's father offers the fatalistic teleology that "we were born to die" (*Romeo and Juliet* III:iv, 4). For Caesar, death's inescapability is a manifest argument for bravery.

Cowards die many times before their deaths;
The valiant never taste of death but once.
Of all the wonders that I yet have heard,
It seems to me most strange that men should fear;
Seeing that death, a necessary end,
Will come, when it will come.

(*Julius Caesar* II:ii, 32–37)

Hamlet, however, finds little consolation that "'t is common; all that lives must die, / Passing through nature to eternity" (*Hamlet* I:ii, 72–73). Richard II bemoans, "Cry woe, destruction, ruin, decay: / The worst is death, and

death will have his day" (*Richard II* III:ii, 102–103). His awareness of death's necessity does not instill acceptance.

Cultures in the past and present alike have turned to religion to reconcile the uncertainty and powerlessness which envelop death. Indeed, the nature of one's beliefs (secular or theological) helps to determine whether death is perceived as a final end or a new beginning. Ideally, a "synergism of religion and medicine," forged by an open attitude toward others' views, will ease the process.[2(p235)]

Regret

"O, our lives' sweetness! / That we the pain of death would hourly die, / Rather than die at once!" (*King Lear* V:iii, 185–187). Life's succulent beauty, not death's fearsome repugnance, sings in these words. Disappointment is a natural reaction to the untimely forfeiture of the gift of life. When one's behavior (for example, smoking and lung cancer) leads to illness, a person may regret his actions. Moreover, one might regret abandoning unrealized goals or unresolved relationships. Most of us hope to leave a lasting legacy through our efforts, but the acknowledgment of a foreshortened future may make our achievements seem dwarfed by our intentions.

After Laertes treacherously stabs Hamlet with an envenomed fencing foil, he reveals before his own death, "Hamlet, thou art slain; / No medicine in the world can do thee good; / In thee there is not half an hour of life" (*Hamlet* V:ii, 321–323). Hamlet is finally spurred toward his revenge by the knowledge of his imminent demise. Though long preoccupied with thoughts of death, in the end Hamlet longs for life.

> I am dead, Horatio....
> Had I but time, (as this fell sergeant, death,
> Is strict in his arrest,) O! I could tell you,—
> But let it be....
> ...what a wounded name,
> Things standing thus unknown, shall live behind me!
> If thou didst ever hold me in thy heart,
> Absent thee from felicity awhile,
> And in this harsh world draw thy breath in pain,
> To tell my story....
> ...The rest is silence.
> (*Hamlet* V:ii, 341, 344–346, 352–357, 366)

Loneliness

Feelings of isolation and emptiness are common as death nears. The dying individual may feel misunderstood, excluded, or afraid of dying alone. Loneliness may result from fewer visits from family and friends, imparting a feeling of incarceration: "I have been studying how I may compare / This prison, where I live, unto the world: / And for because the world is populous, / And here is not a creature but myself, / I cannot do it" (*Richard II* V:v, 1–5). The end of another's life may remind us of our own mortality, as Juliet's death did Lady Capulet: "O me! this sight of death is as a bell, / That warns my old age to a sepulchre" (*Romeo and Juliet* V:iii, 206–207).

King Lear, accustomed to a majestic entourage (but now in retirement and expecting his daughters' charity), deplores his loneliness. "No seconds? All myself? / Why, this would make a man a man of salt, / To use his eyes for garden water-pots, / Ay, and laying autumn's dust.... / I will die bravely, like a smug bridegroom" (*King Lear* IV:vi, 194–198). Later, briefly reunited with his loyal daughter Cordelia, he imagines a paradise of parental love:

> Come, let's away to prison;
> We two alone will sing like birds i' the cage:
> When thou dost ask me blessing, I'll kneel down,
> And ask of thee forgiveness. So we'll live,
> And pray, and sing, and tell old tales, and laugh
> At gilded butterflies, and hear poor rogues
> Talk of court news;...
> And take upon's the mystery of things,
> As if we were God's spies:
> (*King Lear* V:iii, 8–14, 16, 17)

In his last moments of life, Lear forsakes his pride and finds redemption through his daughter.

Physicians may unintentionally contribute to the loneliness and frustration of dying patients, in that "[m]anaging the end of human life requires many skills that are commonly scattered between different specialties."[9(p1777)] This may lead patients to view their care as fragmented and impersonal. Indeed, "feelings of discomfort may lead physicians [to] create a safe emotional distance from their patients."[10(p236)] While some solitude may be desired, a physician's support can help patients feel connected rather than abandoned.

Loss of Autonomy and Dignity

In a society that values self-determination, many individuals fear that the circumstances of dying will strip them of their personhood and sense of control. Juliet's pledge of loyalty eases her mind, because "[i]f all else fail, myself have power to die" (*Romeo and Juliet* III:v, 242). Such desperate solutions may be avoided by involving patients in their care. Indeed, "[a]utonomy in patients' decision making is now the irresistible trend, [though m]any doctors fear this challenge to their own previous secure and powerful autonomy."[9(p1777)] Do not resuscitate (DNR) orders, living wills, and advance directives can temper the "frenetic medical tour de force" of cardiopulmonary resusciation.[11(p1627)] When properly used, such documents can be powerful tools for honoring the wishes of our patients.[4] However, a recent study found that half of physicians did not know about or respect their patients' advance directives.[12]

Some may worry that dehumanizing medical technology will detract from their dignity.[13] In Shakespeare's time, dignity was strongly associated with soundness of mind and strength of youth, which can be compromised by age and approaching death:

> It is too late: the life of all his blood
> Is touch'd corruptibly; and his pure brain

(Which some suppose the soul's frail dwelling-house)
Doth, by the idle comments that it makes,
Foretell the ending of mortality....
O vanity of sickness!...
Death, having prey'd upon the outward parts,
Leaves them, invisible; and his siege is now
Against the mind
(*King John* V:vii, 1–5, 13, 15–17)

Similarly, the dying Lear says, "I fear, I am not in my perfect mind" (*King Lear* IV:vii, 63). These sentiments are also reflected in a poem describing the roles we play on the stage of life: "Last scene of all, / that ends this strange eventful history / Is second childishness, and mere oblivion: / Sans teeth, sans eyes, sans taste, sans everything" (*As You Like It* II:vii, 163–166).

Suicide

Suicide is a common topic on Shakespeare's stage. Some tragic protagonists (Lear, Hamlet, Macbeth) willingly set foot on the path that predictably leads to their demise. Others are the actual instruments of their deaths. Romeo and Othello commit suicide in the heat of emotion, with little forethought. In contrast, characters who contemplate suicide over time are depicted as emotionally imbalanced. Hamlet is preoccupied with suicidal ideation, as evidenced by the soliloquies above and his half-comic exchange with Polonius:

Polonius: My honorable lord, I will most humbly take my leave of you.
Hamlet: You cannot, sir, take from me anything that I will more willingly part withal; except my life, except my life, except my life.
(*Hamlet* II:ii, 213–15)

Hamlet's Ophelia drowns herself, mad with grief over the accidental death of her father. Lear's ally Gloucester, blinded by his enemies, attempts to end his own life; he feels that his suicide attempt is morally wrong but rationalizes it by his desolate state:

O you mighty gods!
This world I do renounce, and in your sights
Shake patiently my great affliction off;
If I could bear it longer, and not fall
To quarrel with your great opposeless wills,
My snuff, and loathed part of nature, should
Burn itself out.
(*King Lear* IV:vi, 34–39)

Gloucester's suicide attempt goes awry, and he attributes his survival to divine intervention. Spirits bolstered, he states "...henceforth I'll bear / Affliction till, it do cry out itself / 'Enough, enough,' and die.... You ever-gentle gods, take my breath from me: / Let not my worser spirit tempt me again / To die before you please!" (*King Lear* IV:vi, 75–77, 216–218). A dramatic parallel to Lear, this wretched character is redeemed as he comes to understand the sanctity and stewardship of life.

In the face of issues such as physician-assisted suicide, we continue to reevaluate the role of physicians in caring for patients at the end of life.[14,15] Indeed, this debate may be fueled by a lack of public confidence in the medical profession to deliver palliative care. In a recent survey, about a third of responding physicians expressed a willingness to help end a patient's life by providing or administering drugs; 18% had received requests for assisted suicide and 6% had acceded.[16] Our common sense should be at least as valuable a guide as the legal system, lest we become relegated to a role analogous to Romeo's wretched apothecary. Building on the play's themes of haste and rash impetuousness, his "poverty, but not [his] will, consents" to sell Romeo "a dram of poison;... As will disperse itself through all the veins, / That the life-weary taker may fall dead; / And that the trunk may be discharg'd of breath / As violently, as hasty powder fir'd / Doth hurry from the fatal cannon's womb" (*Romeo and Juliet* V:i, 75, 60–65). Compassionate and appropriate care can prevail when we understand and honor our patients' values.

Appropriate Death

The concept of an appropriate death consists of care, communication, composure, continuity, control, and closure.[17] A dignified death, characterized by a minimum of suffering and conflict, should be the goal when treatment becomes ineffective or overly burdensome. Ideally, the dying patient will indicate that his care has been suitable and that he expects and accepts death.[18]

King Lear depicts a Shakespearean precedent of appropriate death. Gloucester, thwarted in his suicide attempt, cries, "[i]s wretchedness depriv'd that benefit, / To end itself by death? 'T was yet some comfort, / When misery could beguile the tyrant's rage, / And frustrate his proud will" (*King Lear* IV:vi, 61–64). Lear, upon awakening from a long swoon, says

You do me wrong to take me out o' the grave.—
Thou art a soul in bliss; but I am bound
Upon a wheel of fire, that mine own tears
Do scald like molten lead....
I am mightily abus'd.—I should even die with pity,
To see another thus.—I know not what to say.
(*King Lear* IV:vii, 45–48, 53–54)

After Lear's death, his allies are admonished against attempting to revive him. "Vex not his ghost: O, let him pass! he hates him / That would upon the rack of this tough world / Stretch him out longer.... The wonder is, he hath endur'd so long: / He but usurp'd his life" (*King Lear* V:iii, 314–318). The same sentiment might apply when physicians' goals supersede those of their patients, for example by heroically restoring normal sinus rhythm to a 90-year-old with a painful terminal disease.

Perhaps in some circumstances, we should "go gently into that good night."[19] "Just death, kind umpire of men's miseries" (*King Henry* VI, Part One II:v, 29), can represent a welcomed end to suffering or to the futility of a vegetative existence. Physicians have the opportunity to let their patients die "in a manner consonant with [their own] values and coping mechanisms."[10] In many cases, home care or hospice (which center on comfort, counseling, and family support) would be the best option, and timely discussions and referrals by physicians are essential.[20]

Bereavement

Bereavement, the objective state of one who has lost a significant person to death, is a time of physical and mental vulnerability,[21] when physicians shift their focus toward the family. Two aspects of bereavement, grief and memorialization, are discussed below.

Grief

Embodied in physical and emotional symptoms,[7] grief is a natural and necessary part of bereavement. Indeed, "[t]o weep is to make less the depth of grief" (*King Henry* VI, Part Three II:i, 85). Three stages of grief have been described: shock and disbelief, longing for and preoccupation with the deceased, and finally a resolution and resumption of one's life.[22]

Emotional shock may be precipitated by the realization that the deceased will no longer be present to do those things that defined his or her character. "Dost thou lie so low? / Are all thy conquests, glories, triumphs, spoils, / Shrunk to this little measure?" (*Julius Caesar* III:i, 148–150). Accordingly, survivors must adjust to the deceased's absence. This sentiment is famously eulogized by Hamlet as he holds a jester's skull in the graveyard.

> Alas, poor Yorick!—I knew him, Horatio: a fellow of infinite jest, of most excellent fancy: he hath borne me on his back a thousand times; and now, how abhorred my imagination is! my gorge rises at it. Here hung those lips, that I have kissed I know not how oft. Where be your gibes now? your gambols? your songs? your flashes of merriment, that were wont to set the table on a roar?
>
> (*Hamlet* V:i, 191–197)

Some of Shakespeare's great heroes are motivated to action after a dramatic pause of mourning. In the following excerpt, Hamlet is chided by his uncle (and now stepfather).

> 'T is sweet and commendable in your nature, Hamlet,
> To give these mourning duties to your father:
> But, you must know, your father lost a father;
> That father lost, lost his; and the survivor bound
> In filial obligation, for some term,
> To do obsequious sorrow: but to persever
> In obstinate condolement, is a course
> Of impious stubbornness; 't is unmanly grief;
>
> (*Hamlet* I:ii, 87–94)

An appeal to uphold a masculine stoicism is reiterated to the disconsolate Romeo, who is reprimanded that his "tears are womanish" (*Romeo and Juliet* III:iii, 110). Juliet is scolded for mourning her cousin Tybalt: "What! wilt thou wash him from his grave with tears? / An if thou couldst, thou couldst not make him live: / Therefore, have done. Some grief shows much of love; / But much of grief shows still some want of wit" (*Romeo and Juliet* III:v, 69–74).

In his own voice, Shakespeare repudiates prolonged grief. "No longer mourn for me when I am dead, / Than you shall hear the surly sullen bell / Give warning to the world that I am fled / From this vile world, with vilest worms to dwell" (Sonnet 71). The passage serves as a reminder that a dying person may feel anxiety and guilt as the source of loved ones' anticipatory sorrow.

Of course, it is important to "[g]ive sorrow words; [for] the grief, that does not speak, / Whispers the o'er-fraught heart, and bids it break" (*Macbeth* IV:iii, 210–211). Physicians can help by "combining scientific information with a warm and caring approach",[7(p266)] and by drawing on the expertise of nurses and other staff. While reassuring families that grief is a normal experience, signs of abnormal grief (such as decreased self-esteem, suicidal thoughts, and functional impairment) merit attention.[7]

In time, grief must end, as "[w]hat's gone and what's past help, / Should be past grief" (*The Winter's Tale* III:ii, 222–223). Successful resolution of grief can bring closure and restore a sense of freedom to survivors.[7] In resuming one's normal life, emotional energy must be withdrawn from the deceased and reinvested in other relationships and activities.[22]

Memorialization

As a final stage of bereavement, an eduring mental representation of the deceased is shaped by drawing upon past experiences.[22] For example, Hamlet vows to "wipe away all trivial fond records" from the table of his memory to honor his father (*Hamlet* I:v, 98–99). In addition to preserving cherished attributes, memorialization can ease the task of detachment.

Juliet prophetically offers the image by which she would remember her paramour. "Give me my Romeo: and, when he shall die, / Take him and cut him out in little stars, / And he will make the face of heaven so fine, / That all the world will be in love with night / And pay no worship to the garish sun" (*Romeo and Juliet* III:ii, 21–25). Ariel's song describes another memorialization. "Full fathom five thy father lies; / Of his bones are coral made; / Those are pearls that were his eyes; / Nothing of him that doth fade, / But doth suffer a sea-change / Into something rich and strange" (*The Tempest* I:ii, 398–403). Each passage involves a transformation into something less ephemeral than the human form.

Romeo also offers a memorialization when, mistaking Juliet's unconsciousness for death, he wishes her form to be forever preserved as a paragon of beauty.

> Death, that hath suck'd the honey of thy breath
> Hath had no power yet upon thy beauty:

Thou art not conquer'd; beauty's ensign yet
Is crimson in thy lips, and in thy cheeks,
And death's pale flag is not advanced there....
Why art thou yet so fair? Shall I believe
That unsubstantial death is amorous;
And that the lean abhorred monster keeps
Thee here in dark to be his paramour?
(*Romeo and Juliet* V iii, 92–96, 102–105)

Conclusion

In this essay, I have endeavored to find common ground between the worlds of Shakespeare and clinical medicine to offer practitioners a fresh perspective. Interested readers are encouraged to refer to Shakespeare's plays to restore his thoughts to their original context. Understanding and responding to the emotional state of dying patients is important because psychosocial factors can influence the prognosis and especially the quality of life.[23] Therefore, "open communication, an empathetic spirit, and a desire to be helpful"[2(p235)] are appropriate goals as we work with patients and families. At the same time, it is well to remember that the healing power of medicine must ultimately succumb to mortality and that dying patients need our honesty and respect at least as much as impersonal technological interposition.

Acknowledgments

Gail Furman, PhD, Tom Throckmorton, MD, Carolyn Walling, MA, and Abigail Walling provided helpful suggestions and support.

REFERENCES

1. Cassel CK, Vladeck BC. ICD-9 code for palliative or terminal care. N Engl J Med 1996; 335:1232–1234

2. Parmley WW. The face of death: grim reaper or rite of passage? J Am Coll Cardiol 1996; 27:234–235

3. Miller FG, Finns JJ. A proposal to restructure hospital care for dying patients. N Engl J Med 1996; 334:1740–1742

4. Loewy EH. Ethical considerations in executing and implementing advance directives. Arch Intern Med 1998; 158:321–324

5. Gross MD. What do patients express as their preferences in advance directives? Arch Intern Med 1998; 158:363–365

6. Walling HW. Life's brief candle: a Shakespearean guide to death and dying for compassionate physicians. West J Med 1997; 166:280–284

7. Krigger KW, McNeely JD, Lippmann SB. Dying, death, and grief: helping patients and their families through the process. Postgrad Med 1997; 101:263–270

8. John Milton. Paradise Lost. II:146–151

9. Managing a comfortable death. Lancet 1996; 347:1777

10. McCormick TR, Conley BJ. Patients' perspectives on dying and on the care of dying patients. West J Med 1995; 163:236–243

11. Ciaglia P. From CPR to DNR: the return of death with dignity. Chest 1996; 10:1627

12. The SUPPORT Principal Investigators. A controlled trial to improve care for seriously ill hospitalized patients. JAMA 1995; 274:1591–1598

13. Geppert CMA. The rehumanization of death: the ethical responsibility of physicians to dying patients. JAMA 1997; 277:1408–1409

14. Drickamer MA, Lee MA, Ganzini L. Practical issues in physician-assisted suicide. Ann Intern Med 1997; 126:146–151

15. Emanuel LL. Facing requests for physician-assisted suicide: toward a practical and principled clinical skill set. JAMA 1998; 280:643–647

16. Meier DE, Emmons C-A, Wallenstein S, Quill T, Morrison RS, Cassel CK. A national survey of physician-assisted suicide and euthanasia in the United States. N Engl J Med 1998; 338:1193–1201

17. Weisman AD. Coping With Cancer. New York, McGraw Hill, 1979

18. Weisman AD. Coping with untimely death. Psychiatry 1973; 36:366–378

19. Dylan Thomas. "Do Not Go Gentle Into That Good Night"

20. Steel K. Increased attention to pain and dying. Arch Int Med 1997; 157:924–925

21. Spratt ML, Denney DR. Immune variables, depression, and plasma cortisol over time in suddenly bereaved parents. J Neuropsych Clin Neurosci 1991; 3:299–306

22. Dane BO. Anticipatory mourning of middle-aged parents of adult children with AIDS. Fam Soc 1991; 72:108–115

23. Creagan ET. Attitude and disposition: do they make a difference in cancer survival? Mayo Clinic Proc 1997; 72:160–163

ERRATUM

In the May 1998 issue, the title page for the "Final Report of the Commission on the Future of Medical Education"[1] was omitted from the final publication. The names of the authors of the report, Charles B. Wilson, MD, MSHA, Senior Associate to the President, and Arlyss L. Anderson, RN, MS, PNP, University of California, San Francisco, should have been included.

REFERENCE

1. Wilson CB, Anderson AL. Final Report of the UC Commission on the Future of Medical Education. West J Med 1998 May; 168:445–482

Poem

* * *

Bad News—

from the starch of my white armor
across a moat of polished oak;
you balance between an indrawn gasp
and a grunt of pain.

Myself, I'd as soon not be here. I could drown
in the terror on your face. You are looking
into places I can't see, I want to drop the news fast
and cold, cut my anchor line and run.

I might play this out as comedy, "The good news:
you are going to die," but neither of us
could wear the baggy pants. Somewhere
a nervous actor pleads "Come on, kids,

put on a show, things will work out swell."
Supporting hope against the odds is hard
harder still to hold the silence,
the waiting of your need.

Catharine Clark-Sayles
Mill Valley, California

Classified Advertisements

The rate for each insertion is **$1.50 per word, with a 30 word ($45) minimum.** Confidential box number charge: $10 each month.
A word is defined as one or more letters bounded by spaces. The following gives some examples:

Linda H. Clever, MD	= 4 words	allergy/immunology	= 1 word
Send CV	= 2 words	Sacramento, CA 95817	= 3 words
A	= 1 word	804-979-8034	= 1 word
February 22, 1997	= 3 words		

Classified display rate $70 per inch. Maximum sizes: 1 column by 5" or 2 columns by 2" (2-1/8" per column). Larger classified ad space by special arrangements.
Copy for classified advertisements should be received not later than **first of the month preceding issue. All copy must be typed or printed.** Classified advertisers using Box Numbers forbid the disclosure of their identity; your inquiries in writing will be forwarded to Box Number advertisers. Although *The Western Journal of Medicine* believes the classified advertisements in these columns to be from reputable sources, we do not investigate the offers made and assume no liability concerning them. The right is reserved to reject, withdraw, or modify all classified advertising copy in conformity with the decisions of the Advertising Committee.

Please Type or Print Advertising Copy

Classified Advertisements Are Payable in Advance
CLASSIFIED ADVERTISEMENTS, THE WESTERN JOURNAL OF MEDICINE
2 WEST TAUNTON AVENUE, BERLIN, NJ 08009
(609) 768-9360; FAX (609) 753-0064
Ads may be placed online at www.wjmed.com

IDAHO

Make One Of America's Best Places to Live Even Better.

Where You'll Work.
Primary Health, Idaho's largest, fastest-growing integrated health care system whose network of family medicine immediate care centers, by-appointment family practitioners, pediatricians and OB/GYNs serves beautiful southern Idaho.

Where You'll Live.
In a great place to raise a family with quality schools, incredible outdoor recreation and a rural atmosphere close to a metropolitan area with a beautiful performing arts center, excellent hospitals and professional sports.

What You'll Get.
The financial backing and medical resources of a major health care network. A competitive salary, ownership options, flexible work and call schedules, professional growth, full benefits including medical and dental and much more.

Submit CV and questions to:
BECKY NELSON
(800) 688-5008 ext. 507 • FAX (208) 344-4262
Physician Recruitment
800 Park Boulevard, Suite 760
Boise, Idaho 83712

Primary Health

CALIFORNIA

Int-Im PHYSICIANS

LOCUM TENENS
PERMANENT PLACEMENTS

Jim Ellis (800) 437-7676

PHYSICIANS WANTED

FAMILY PRACTICE - MILWAUKEE, WISCONSIN LAKESIDE: Join two board certified family physicians in a unique practice opportunity-integrated health care for women and their families with a health plan focused on wellness through holistic, preventative programs including yoga, acupuncture, massage, stress management, etc. OB is optional, excellent and flexible call arrangement, teaching opportunities also available. Brand new beautiful clinic with a unique design, comprehensive benefit package. Call Laurie Myers, 800-338-7107 or fax CV 414-427-7251 or e-mail: fha@execpc.com

The Western Journal of Medicine

www.wjmed.com

Practical Information for Practicing Physicians

PHYSICIANS WANTED

INTERNAL MEDICINE, INPATIENT (BAKERSFIELD, CA) - At Kaiser Permanente in Southern California, the excellence of our physicians is reflected in the quality of our health care. Currently, we have an excellent opportunity at our Bakersfield location for an Internist with board certification and inpatient exp. At Kaiser, you'll enjoy the resources & rewards of an industry leader, outstanding compensation & benefits and the opportunity to be part of a dynamic medical group providing health care services to over 2.5 million members in Southern California. For more information, call (800) 541-7946 or send CV to: Kaiser Permanente, SCPMG, Dept. ADVE, Walnut Center, Pasadena, CA 91188-8013, FAX (626) 405-2675.

CALIFORNIA, NORTHERN - Internist needed for 80+ physician group affiliated with Catholic Healthcare West. Hospital and office based practice (50-50) with shared call, competitive income and benefits. Contact: Danise Cooper, 1-800-765-3055, ID#: 6118WE, Fax: 314-726-3009. Visit our website at www.cejka.com

OCCUPATIONAL MEDICINE Locum Tenens Pacific Northwest - Northwest Permanente, P.C., a physician-managed, multispecialty group, has a full-time, six-month to one-year locum tenens opportunity available for a Board Certified and/or residency trained occupational medicine physician or other relevant primary care trained physician, at our medical offices in Oregon and Southwest Washington. Our Occupational Health Program has 19 physicians and covers outpatient clinics at nine sites with 65,000 visits per year, an Employee Health Service, and an Environmental Safety Program serving nearly 6,000 employees. We offer a competitive salary and benefit package which includes family medical insurance, paid time off, professional liability coverage, and a relocation allowance. Please forward C.V. to: W.J. Clark, Director of Professional Resources, NORTHWEST PERMANENTE, P.C., 500 NE Multnomah St., Suite 100, Portland, OR 97232-2099. (800) 813-3763. EOE.

OREGON AND THE NORTHWEST. Urban, suburban, rural locations; variety of practice arrangements; all specialties. Placement professionals for 20 yrs. Oberto & Associates, 920 Pinecrest Terr, Ashland, OR 97520. (800) 482-6656; FAX (541) 482-4951. No J-1 Opp. boberto@jeffnet.org.

Reprints

Any article printed in *WJM* can be purchased in quantities of 100 or more. Printed on fine quality journal stock. Prices are based upon article length and quantity ordered.

Call Walter Finley for prices and information,
8:30 – 5:30 EST, Mon– Fri,
(804) 979-8034 ext. 146;
or E-Mail to: wjm@cjp.com

POSITIONS WANTED

EXPERIENCED ENT PHYSICIAN, fifteen years busy clinical practice, completing allergy/rhinology fellowship June 1999. Seeks California practice opportunity (Los Angeles, Orange County, California coast, San Diego, San Francisco). Phone (573) 447-1485.

Since 1979
the

Interim PHYSICIANS.

LOCUM TENENS NETWORK has been taking the hassles of the paperwork and overhead out of practicing medicine. Practice near home or travel the country. We will coordinate all your travel details and provide you with the best occurrence malpractice policy available. Explore a partnership with Interim Physicians and open new horizons for your future.

Call today! (800) 333-7828

MEETINGS/CONFERENCES

Fourth Annual Cardiology at Cancun 1999 February 22-26, 1999. Cancun, Mexico. 27 Category 1 credit hours. Fees before February 8: $590 for ACC members; $695 for non-members; $485 for fellows-in-training, residents, nurses, physician assistants, and technologists. Additional $50 after February 8. For information, call American College of Cardiology, Extramural Programs, 800-253-4636, ext. 695; (outside U.S. and Canada, 301-897-5400, ext. 695); FAX 301-897-9745.

Fifteenth Annual Cardiovascular Conference at Lake Louise. March 28 - April 1, 1999. Lake Louise, Alberta, Canada. 16.5 Category 1 credit hours. Fees before March 15: $495 for ACC members; $600 for non-members; $295 for fellows-in-training, residents, nurses, physician assistants, and technologists. Additional $50 after March 15. For information, call American College of Cardiology, Extramural Programs, 800-253-4636, ext. 695; (outside U.S. and Canada, 301-897-5400, ext. 695); FAX 301-897-9745.

ADVERTISING INDEX

eBMJ . . . . . 2nd Cover
SOUTHERN MEDICAL ASSOCIATION . . . . . 3rd Cover
CLINICAL EVIDENCE ORDER FORM . . . . . 4th Cover
BMJ QUALITY IMPROVEMENT CONFERENCE . . . . . Page 72

The California Academy of Family Physicians invites you to attend our 51st Annual Scientific Assembly February 12-14, 1999 in Beautiful San Diego

Featuring:

- A keynote address by Nancy Dickey, MD, President of the American Medical Association & Family Physician
- 9 clinical lectures on a wide array of topics
- 4 procedural workshops
- 5 practice management/clinical seminars
- An unforgettable drama about teen health concerns
- Panel discussion on implications of genetic testing
- 6 interactive, open discussion forums
- Preconference Internet and Smart Coding seminars
- 9 satellite CME Sessions at no additional cost

Receive up to 43.5 hours of CME Credit

Outstanding Workshops & Seminars

CALIFORNIA ACADEMY OF FAMILY PHYSICIANS

For details and registration info, call 415-394-9121
Or — register online at www.FamilyDocs.org/Register

The Western Journal of Medicine

Practical Information for Practicing Physicians

Subscribe Now!

The Western Journal of Medicine extends its thanks to the loyal CMA members who have already made their commitment by subscribing to *WJM*. Here is your opportunity to support the revitalized *Journal*...**now available through subscription only.**

Your subscription to *WJM* features:

EPITOMES
Highlights of major advances in a different specialty each month with brief epitomes by experts in the field.

BIOMEDICAL SCIENCE
Five clinical research societies coordinate important new research findings, emphasizing clinical value.

SOCIOECONOMICS
WJM is often the first to predict, examine, and evaluate socioeconomic changes and trends.

CONFERENCES
All you need to know about medical conferences, nationally and locally.

EDITORIAL LEADERSHIP
Linda Hawes Clever, MD, will extend *WJM's* reach and impact in medical circles around the world.

The future of *WJM* is brighter than ever. Subscribe now so you won't miss a single monthly issue. Only **$45** per year for affiliated association members (**$65** for regular subscribers).

There are four easy ways to subscribe...

1 ***Call (804) 817-2000*** or

2 ***Fax this ad to (804) 817-2020*** or

3 ***Sign up online at www.wjmed.com*** or

4 ***Mail this ad to the address below***

...and there are three easy ways to pay:

Charge my: ☐ Visa ☐ MasterCard ☐ Check enclosed ☐ Bill me

Name on card _____

Card # _____ Exp. Date

Signature _____

Name _____

Address _____

City, State, Zip _____

Phone _____

Fax _____ E-Mail

The Western Journal of Medicine

Check One (12 issues):

☐ $45 Member Rate

☐ $65 Regular Rate

☐ $20 Student/Resident/Intern

☐ $90 Institutional Rate

Return to: *The Western Journal of Medicine*, 1224 West Main Street, Suite 200, Charlottesville, VA 22903-2858.
Phone (804) 817-2000. Fax (804) 817-2020.

LACMA

INVITATION TO DELEGATES

A Three Day Conference
Tuesday 25 - Thursday 27 May 1999
STOCKHOLM INTERNATIONAL FAIRS
SWEDEN

4th European Forum on Quality Improvement in Health Care and 4th Swedish QUL Conference

THEMES OF THE FORUM

- *Accelerating clinical improvement*
- *Quality improvement in primary care*
- *Making health better in the community*
- *Promoting evidence - based health care*
- *Building partnerships with patients*
- *Measurement for quality improvement in health care*
- *Leading change*
- *Increasing access and reducing delay in health care*
- *Harnessing information and communication technology for health improvement*
- *Putting quality improvement at the heart of education of health care professionals*

AIMS OF THE FORUM

- *To provide education on how to improve health care*
- *To exchange sound, practical ideas on improving health care*
- *To provide a setting for deep discussion and shared learning among those charged with leading improvements in health care*
- *To build the scientific base of methods to improve health care*

Book your place by 31 January 1999 and save £50 on the full registration fee

PRINCIPLES OF THE FORUM

- *Emphasis on what works*
- *Learning through experience*
- *Concentrating on improvement rather than inspection*
- *Patient orientation*
- *Multidisciplinary*
- *Basing change on measurement*
- *Team orientation*
- *Cost consciousness*
- *Encouraging efficiency*
- *All teach, all learn*

FOR FURTHER INFORMATION, PLEASE COMPLETE AND RETURN THE FORM BELOW.

Supported by

Please send me further details on the 4th European Forum on Quality Improvement in Health Care and 4th Swedish QUL Conference.

Name: _____

Address: _____

_____

_____

Postcode: _____ Country: _____

Job/Position: _____

Telephone: _____ Fax: _____

E-mail: _____ 7603 26

Please return this form to Marchella Mitchell, BMA/BMJ Conference Unit, PO Box 295, London, WC1H 9TE.
Fax: +44 (0) 171 383 6869 Email: MMitchell@bma.org.uk

1999 EDUCATIONAL CALENDAR

SOUTHERN MEDICAL ASSOCIATION

Your CME Resource!

ruary 19-21	**2nd Annual Conference on Osteoporosis: Diagnosis, Treatment and Prevention in Primary Care** Indian River Plantation Marriott Stuart, Florida
rch 4-6	**Southern Orthopaedic Association's 9th Annual SEC Sports Medicine Symposium** Atlanta Hilton and Towers Atlanta, Georgia
rch 12-14	**4th Conference on Pain Management: Strategies for Improving Outcomes** Sandestin Beach Hilton Destin, Florida
rch 26-28	**New Drugs Update 1999** Hyatt Regency Hilton Head Hilton Head Island, South Carolina
rch 27- April 3	**Southern Orthopaedic Association's Hot Topics in Cold Weather II** Snowmass Resort Snowmass, Colorado
ril 9-11	**Management Challenges in Chronic Diseases** Marriott Sawgrass Resort Ponte Vedra, Florida
ril 9-11	**Spring Managed Care Update** Westin Hilton Head Hilton Head Island, South Carolina
y 21-23	**Hot Topics in Primary Care** Marriott Marina Ft. Lauderdale, Florida
ne 11-13	**3rd Annual Conference on Hypertension** The Inn at Kiawah Island Resort Kiawah Island, South Carolina
ne 13-16	**23rd Annual Sea Island Symposium on Lung Diseases** The Cloister Sea Island, Georgia
ne 25-27	**4th Annual Meeting of the Southern Association for Primary Care** Chateau on the Lake Resort Branson, Missouri
July 9-11	**8th Conference on General Surgery and Gastroenterology** The Cloister Sea Island, Georgia
July 12-15	**10th Annual Focus on the Female Patient** Kiawah Island Resort Kiawah Island, South Carolina
July 15-17	**16th Annual Meeting of the Southern Orthopaedic Association** The Ritz-Carlton Amelia Island Amelia Island, Florida
July 16-18	**Pediatric & Adolescent Medicine Update** Kiawah Island Resort Kiawah Island, South Carolina
August 5-7	**12th Annual Meeting of the Southern Association for Oncology** Hamilton Princess Hamilton, Bermuda
August 19-21	**Infectious Diseases Conference: An Update for Primary Care Physicians** The Peaks Resort and Spa Telluride, Colorado
August 27-29	**Focus on the Older Patient** The Ritz-Carlton Amelia Island Amelia Island, Florida
August 28-29	**4th Annual Managed Care Conference** Omni Royal Orleans New Orleans, Louisiana
September 17-19	**2nd Annual Conference on Diabetes: Advances in Management & Prevention** Kingsmill Resort Williamsburg, Virginia
November 10-14	**93rd Annual Scientific Assembly of the Southern Medical Association** Wyndham Anatole Hotel Dallas, Texas
December 3-5	**12th Annual Region IV Burn Seminar** Adam's Mark Winston Plaza Winston-Salem, North Carolina

Please call SMA's Education Department at 800-423-4992 for further information on any of these excellent meetings!

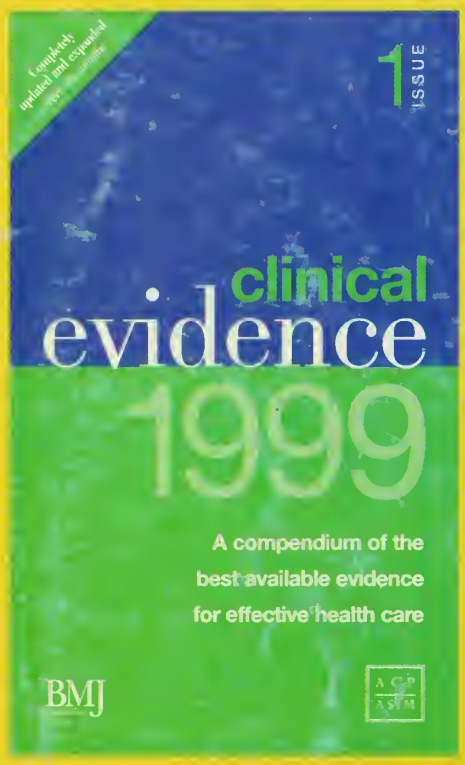
***Check us out!* * www.sma.org * On-line CME!**

NEW

Clinical Evidence

from BMJ Publishing Group

FIRST ISSUE AVAILABLE SPRING 1999



Early Bird Discount by ordering before end of 1998

Clinical Evidence is a compendium of evidence on the benefits and harms of common clin interventions. Written by practising clinicians using rigorous searching and evaluation methods, it will be issued every six months to bring you the most reliable and up-to-date findings on important questions in clinical practice. Clinical Evidence will be published as a convenient pocket-sized book in order to make clinical effectiveness accessible and possible for the majority of health professionals in the UK.

Clinical Evidence will enable clinicians and health care professionals to make informed decisions about:

- Choosing one treatment or test over another
- Informing patients and their families, and involving them in decision making
- Identifying gaps in the evidence
- Conducting and commissioning research
- Auditing clinical procedures
- Resolving disputes over efficacy of treatment
- Training clinicians, managers and students

The first issue will contain:

- Breast Diseases
- Cardiovascular Diseases
- Child Health
- Critical Care
- Diabetes
- Digestive System Diseases
- Diseases of Ear, Nose & Throat
- Effective Communication
- Endocrine Diseases
- Eye Diseases
- Gynaecological Disorders
- Infectious Diseases
- Mental Health
- Musculoskeletal Diseases
- Neurological Diseases
- Perioperative Care
- Pregnancy & Childbirth
- Primary Prevention
- Respiratory Diseases
- Screening
- Wounds
- Skin Diseases
- Sexual Health
- Urinary Tract Disorders

Published in pocket book format for ease of use, Clinical Evidence is available by subscription. A sample section of Clinical Evidence is available for you to view on the web at: www.evidence.org. Subscribing couldn't be easier, simply complete the order form below and return with payment to the address provided.

Clinical Evidence
Publication: Six monthly ISSN: 1462-3846
1999 Subscription rate: £35/US$58
Special rate of £30/US$50 if orders received before the end of December 1998

Please tick:

☐ I enclose a cheque for £/$ .....
(Payable to British Medical Journal. Sterling cheques to be drawn on a UK bank account and US dollar cheques on a USA bank account)

☐ Charge my credit card £/$ .....
American Express/Visa/Master Card/Delta/Switch (circle as appropriate)
Start issue from: Spring 99
Cardholders No
☐☐☐☐ ☐☐☐☐ ☐☐☐☐ ☐☐☐☐ ☐☐☐

Expiry Date:.....Switch Issue No:.....

Signature: .....

Name: .....

Job title: .....

Address: .....

.....

Country: .....Postcode: .....

E-mail Address: .....

☐ Please tick if you do not wish your data to be used for direct marketing purposes

☐ Please send me details of the planned international conference on getting evidence into practice

Return to: BMJ Publishing Group, Journals Marketing Department, PO Box 299, London WC1H 9TD, UK
Tel: +44 (0) 171 383 6270 Fax: +44 (0) 171 383 6402
Email: subscriptions@bmjgroup.com

US subscribers may send payment to: BMJ Publishing Group, Box 590A, Kennebunkport, ME 04046, USA Tel: 1-800-2-FON-BMJ Fax: 1-800-2-FAX-BMJ
N.B. Subscribers in the following countries must add tax to the quoted sterling price unless they can provide a registration number:
Italy and Spain - 4% IVA, Ireland - 21% VAT, Germany - 7% MWS, Belgium - 6% TVA/BTW and France - 20.6% IVA.

BMJ Publishing

Visit our website at: www.evidence.org

AC ASI

THE FRANCIS A. COUNTWAY LIBRARY OF MEDICINE
HARVARD MEDICAL LIBRARY-BOSTON MEDICAL LIBRARY